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SON, Leslie, S.; 20147 Laurel Hill Way, Germantown,  
MD 20874 (US).

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(71) Applicant: MEDIUMMUNE, INC [US/US]; 35 West Watkins Mill Road, Gaithersburg, MD 20878 (US).

(72) Inventors: YOUNG, James, F.; 18309 Mockingbird Lane, Darnestown, MD 20874 (US). KOENIG, Scott;

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(54) Title: METHODS OF ADMINISTERING/DOSING ANTI-RSV ANTIBODIES FOR PROPHYLAXIS AND TREATMENT

A

DIQMTQSPST LSASVGDRVT ITCKCQLSVGYMH WYQQKPG 40  
CDR L1

KAPKLLIY DTSKLAS GPSPR FSGSGSGTEF TLTSSLQPD 80  
CDR L2

DFATYYC FQGSGYPFT FGGGTKLEIK 106  
CDR L3

(57) Abstract: The present invention encompasses novel antibodies and fragments thereof which immunospecifically bind to one or more RSV antigens and compositions comprising said antibody fragments. The present invention encompasses methods preventing respiratory syncytial virus (RSV) infection in a human, comprising administering to said human a prophylactically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein a certain serum titer of said antibodies or antibody fragments is achieved in said human subject. The present invention also encompasses methods for treating or ameliorating symptoms associated with a RSV infection in a human, comprising administering to said human a therapeutically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein a certain serum titer of said antibodies or antibody fragments is achieved in said human subject. The present invention further encompasses compositions comprising

B

QVTLRESPGA LVKPTQTLTL TCTFSGFSLS TSGMSVG WIR 40  
CDR H1

OPPGKALEWL A DIWWDDKKDYNPSLKS RLT ISKDTSKNQV 80  
CDR H2

VLKVTNMDPA DTATYYCAR SMITNWYFDV W GAGTTVTVSS 120  
CDR H3

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antibodies or fragments thereof that immunospecifically bind to a RSV antigen, and methods using said compositions for detection or diagnosis a RSV infection.

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NE, SN, TD, TG).

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**METHODS OF ADMINISTERING/DOSING  
ANTI-RSV ANTIBODIES FOR  
PROPHYLAXIS AND TREATMENT**

5        **1. INTRODUCTION**

The present invention relates to compositions comprising antibodies or fragments thereof that immunospecifically bind to a RSV antigen and methods for preventing, treating or ameliorating symptoms associated with respiratory syncytial virus (RSV) infection utilizing said compositions. In particular, the present invention relates to methods for 10 preventing, treating or ameliorating symptoms associated with RSV infection, said methods comprising administering to a human subject an effective amount of one or more antibodies or fragments thereof that immunospecifically bind to a RSV antigen, wherein a certain serum titer of said antibodies or antibody fragments is achieved in said human subject. The present invention also relates to detectable or diagnostic compositions comprising 15 antibodies or fragments thereof that immunospecifically bind to a RSV antigen and methods for detecting or diagnosing RSV infection utilizing said compositions.

2.        **BACKGROUND OF THE INVENTION**

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory 20 tract disease in infants and children (Feigen et al., eds., 1987, *In: Textbook of Pediatric Infectious Diseases*, WB Saunders, Philadelphia at pages 1653-1675; New Vaccine Development, Establishing Priorities, Vol. 1, 1985, National Academy Press, Washington DC at pages 397-409; and Ruuskanen et al., 1993, *Curr. Probl. Pediatr.* 23:50-79). The yearly epidemic nature of RSV infection is evident worldwide, but the incidence and 25 severity of RSV disease in a given season vary by region (Hall, C.B., 1993, *Contemp. Pediatr.* 10:92-110). In temperate regions of the northern hemisphere, it usually begins in late fall and ends in late spring. Primary RSV infection occurs most often in children from 6 weeks to 2 years of age and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall et al., 1979, *New Engl. J. Med.* 300:393-396). Children at increased risk 30 from RSV infection include preterm infants (Hall et al., 1979, *New Engl. J. Med.* 300:393-396) and children with bronchopulmonary dysplasia (Groothuis et al., 1988, *Pediatrics* 82:199-203), congenital heart disease (MacDonald et al., *New Engl. J. Med.* 307:397-400), congenital or acquired immunodeficiency (Ogra et al., 1988, *Pediatr. Infect. Dis. J.* 7:246-249; and Pohl et al., 1992, *J. Infect. Dis.* 165:166-169), and cystic fibrosis (Abman et al.,

1988, *J. Pediatr.* 113:826-830). The fatality rate in infants with heart or lung disease who are hospitalized with RSV infection is 3%-4% (Navas et al., 1992, *J. Pediatr.* 121:348-354).

RSV infects adults as well as infants and children. In healthy adults, RSV causes predominantly upper respiratory tract disease. It has recently become evident that some 5 adults, especially the elderly, have symptomatic RSV infections more frequently than had been previously reported (Evans, A.S., eds., 1989, *Viral Infections of Humans: Epidemiology and Control*, 3<sup>rd</sup> ed., Plenum Medical Book, New York at pages 525-544). Several epidemics also have been reported among nursing home patients and institutionalized young adults (Falsey, A.R., 1991, *Infect. Control Hosp. Epidemiol.* 12:602-608; 10 and Garvie et al., 1980, *Br. Med. J.* 281:1253-1254). Finally, RSV may cause serious disease in immunosuppressed persons, particularly bone marrow transplant patients (Hertz et al., 1989, *Medicine* 68:269-281).

Treatment options for established RSV disease are limited. Severe RSV disease of the lower respiratory tract often requires considerable supportive care, including 15 administration of humidified oxygen and respiratory assistance (Fields et al., eds, 1990, *Fields Virology*, 2<sup>nd</sup> ed., Vol. 1, Raven Press, New York at pages 1045-1072). The only drug approved for treatment of infection is the antiviral agent ribavirin (American Academy of Pediatrics Committee on Infectious Diseases, 1993, *Pediatrics* 92:501-504). It has been shown to be effective in the treatment of RSV pneumonia and bronchiolitis, modifying the 20 course of severe RSV disease in immunocompetent children (Smith et al., 1991, *New Engl. J. Med.* 325:24-29). However, ribavirin has had limited use because it requires prolonged aerosol administration and because of concerns about its potential risk to pregnant women who may be exposed to the drug during its administration in hospital settings.

While a vaccine might prevent RSV infection, no vaccine is yet licensed for this 25 indication. A major obstacle to vaccine development is safety. A formalin-inactivated vaccine, though immunogenic, unexpectedly caused a higher and more severe incidence of lower respiratory tract disease due to RSV in immunized infants than in infants immunized with a similarly prepared trivalent parainfluenza vaccine (Kim et al., 1969, *Am. J. Epidemiol.* 89:422-434; and Kapikian et al., 1969, *Am. J. Epidemiol.* 89:405-421). Several 30 candidate RSV vaccines have been abandoned and others are under development (Murphy et al., 1994, *Virus Res.* 32:13-36), but even if safety issues are resolved, vaccine efficacy must also be improved. A number of problems remain to be solved. Immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. The immaturity of the neonatal immune response 35 together with high titers of maternally acquired RSV antibody may be expected to reduce

vaccine immunogenicity in the neonatal period (Murphy et al., 1988, *J. Virol.* 62:3907-3910; and Murphy et al., 1991, *Vaccine* 9:185-189). Finally, primary RSV infection and disease do not protect well against subsequent RSV disease (Henderson et al., 1979, *New Engl. J. Med.* 300:530-534).

5       Currently, the only approved approach to prophylaxis of RSV disease is passive immunization. Initial evidence suggesting a protective role for IgG was obtained from observations involving maternal antibody in ferrets (Prince, G.A., Ph.D. diss., University of California, Los Angeles, 1975) and humans (Lambrecht et al, 1976, *J. Infect. Dis.* 134:211-217; and Glezen et al., 1981, *J. Pediatr.* 98:708-715). Hemming et al. (Morell et al., eds.,  
10 1986, *Clinical Use of Intravenous Immunoglobulins*, Academic Press, London at pages 285-294) recognized the possible utility of RSV antibody in treatment or prevention of RSV infection during studies involving the pharmacokinetics of an intravenous immune globulin (IVIG) in newborns suspected of having neonatal sepsis. They noted that 1 infant, whose respiratory secretions yielded RSV, recovered rapidly after IVIG infusion. Subsequent  
15 analysis of the IVIG lot revealed an unusually high titer of RSV neutralizing antibody. This same group of investigators then examined the ability of hyperimmune serum or immune globulin, enriched for RSV neutralizing antibody, to protect cotton rats and primates against RSV infection (Prince et al., 1985, *Virus Res.* 3:193-206; Prince et al., 1990, *J. Virol.* 64:3091-3092; Hemming et al., 1985, *J. Infect. Dis.* 152:1083-1087; Prince et al., 1983, *Infect. Immun.* 42:81-87; and Prince et al., 1985, *J. Virol.* 55:517-520). Results of these  
20 studies suggested that RSV neutralizing antibody given prophylactically inhibited respiratory tract replication of RSV in cotton rats. When given therapeutically, RSV antibody reduced pulmonary viral replication both in cotton rats and in a nonhuman primate model. Furthermore, passive infusion of immune serum or immune globulin did not  
25 produce enhanced pulmonary pathology in cotton rats subsequently challenged with RSV.

Recent clinical studies have demonstrated the ability of this passively administered RSV hyperimmune globulin (RSV IVIG) to protect at-risk children from severe lower respiratory infection by RSV (Groothius et al., 1993, *New Engl. J. Med.* 329:1524-1530; and The PREVENT Study Group, 1997, *Pediatrics* 99:93-99). While this is a major  
30 advance in preventing RSV infection, this treatment poses certain limitations in its widespread use. First, RSV IVIG must be infused intravenously over several hours to achieve an effective dose. Second, the concentrations of active material in hyperimmune globulins are insufficient to treat adults at risk or most children with compromised cardiopulmonary function. Third, intravenous infusion necessitates monthly hospital visits  
35 during the RSV season. Finally, it may prove difficult to select sufficient donors to produce

a hyperimmune globulin for RSV to meet the demand for this product. Currently, only approximately 8% of normal donors have RSV neutralizing antibody titers high enough to qualify for the production of hyperimmune globulin.

One way to improve the specific activity of the immunoglobulin would be to

5 develop one or more highly potent RSV neutralizing monoclonal antibodies (MAbs). Such MAbs should be human or humanized in order to retain favorable pharmacokinetics and to avoid generating a human anti-mouse antibody response, as repeat dosing would be required throughout the RSV season. Two glycoproteins, F and G, on the surface of RSV have been shown to be targets of neutralizing antibodies (Fields et al., 1990, *supra*; and Murphy et al.,

10 1994, *supra*). These two proteins are also primarily responsible for viral recognition and entry into target cells; G protein binds to a specific cellular receptor and the F protein promotes fusion of the virus with the cell. The F protein is also expressed on the surface of infected cells and is responsible for subsequent fusion with other cells leading to syncytia formation. Thus, antibodies to the F protein may directly neutralize virus or block entry of

15 the virus into the cell or prevent syncytia formation. Although antigenic and structural differences between A and B subtypes have been described for both the G and F proteins, the more significant antigenic differences reside on the G glycoprotein, where amino acid sequences are only 53% homologous and antigenic relatedness is 5% (Walsh et al., 1987, *J. Infect. Dis.* 155:1198-1204; and Johnson et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:5625-5629). Conversely, antibodies raised to the F protein show a high degree of cross-reactivity among subtype A and B viruses. Beeler and Coelingh (1989, *J. Virol.* 7:2941-2950) conducted an extensive analysis of 18 different murine MAbs directed to the RSV F protein. Comparison of the biologic and biochemical properties of these MAbs resulted in the identification of three distinct antigenic sites (designated A, B, and C). Neutralization

20 studies were performed against a panel of RSV strains isolated from 1956 to 1985 that demonstrated that epitopes within antigenic sites A and C are highly conserved, while the epitopes of antigenic site B are variable.

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A humanized antibody directed to an epitope in the A antigenic site of the F protein of RSV, SYNAGIS®, is approved for intramuscular administration to pediatric patients for

30 prevention of serious lower respiratory tract disease caused by RSV at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is a composite of human (95%) and murine (5%) antibody sequences. See, Johnson et al., 1997, *J. Infect. Diseases* 176:1215-1224 and U.S. Patent No. 5,824,307, the entire contents of which are incorporated herein by

35 reference. The human heavy chain sequence was derived from the constant domains of

human IgG<sub>1</sub> and the variable framework regions of the VH genes or Cor (Press et al., 1970, Biochem. J. 117:641-660) and Cess (Takashi et al., 1984, Proc. Natl. Acad. Sci. USA 81:194-198). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the VL gene K104 with Jκ-4 (Bentley et al., 1980, 5 Nature 288:5194-5198). The murine sequences derived from a murine monoclonal antibody, Mab 1129 (Beeler et al., 1989, J. Virology 63:2941-2950), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks.

Although SYNAGIS® has been successfully used for the prevention of RSV 10 infection in pediatric patients, multiple intramuscular doses of 15 mg/kg of SYNAGIS™ is required to achieve a prophylactic effect. In pediatric patients less than 24 months of age, the mean half-life of SYNAGIS® has been shown to be 20 days and monthly intramuscular doses of 15 mg/kg have been shown to result in a mean ± standard derivation 30 day serum titer of 37 ± 21 µg/ml after the first injection, 57 ± 41 µg/ml after the second injection, 68 ± 15 51 µg/ml after the third injection, and 72 ± 50 µg/ml after the fourth injection (The IMPact RSV Study Group, 1998, Pediatrics 102:531-537). Serum concentrations of greater than 30 µg/ml have been shown to be necessary to reduce pulmonary RSV replication by 100 fold in the cotton rat model of RSV infection. However, the administration of multiple intramuscular doses of 15 mg /kg of antibody is inconvenient for the patient. Thus, a need 20 exists for antibodies that immunospecifically bind to a RSV antigen, which are highly potent, have an improved pharmacokinetic profile, and thus have an overall improved therapeutic profile. Further, a need exists for antibodies that immunospecifically bind to a RSV antigen which require less frequent administration.

Citation or discussion of a reference herein shall not be construed as an admission 25 that such is prior art to the present invention.

### 3. SUMMARY OF THE INVENTION

The present invention is based, in part, on the development of methods for achieving or inducing a prophylactically or therapeutically effective serum titer of an antibody or 30 fragment thereof that immunospecifically binds to a respiratory syncytial virus (RSV) antigen in a mammal by passive immunization with such an antibody or fragment thereof, which methods require lower dosages and/or less frequent administration than previously known methods. The present invention is also based, in part, on the identification of antibodies with higher affinities for a RSV antigen which result in increased efficacy for 35 prophylactic or therapeutic uses such that lower serum titers are prophylactically or

therapeutically effective, thereby permitting administration of lower dosages and/or reduced frequency of administration.

The present invention provides methods of preventing, neutralizing, treating and ameliorating one or more symptoms associated with RSV infection in a subject comprising

5 administering to said subject one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with high affinity and/or high avidity. Because a lower serum titer of such antibodies or antibody fragments is therapeutically or prophylactically effective than the effective serum titer of known antibodies, lower doses of said antibodies or antibody fragments can be used to achieve a

10 serum titer effective for the prevention, neutralization, treatment and the amelioration of symptoms associated with a RSV infection. The use of lower doses of antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens reduces the likelihood of adverse effects. Further, the high affinity and/or high avidity of the antibodies of the invention or fragments thereof enable less frequent administration of said antibodies

15 or antibody fragments than previously thought to be necessary for the prevention, neutralization, treatment or the amelioration of symptoms associated with a RSV infection.

The present invention also provides antibodies which immunospecifically bind to one or more RSV antigens and have increased *in vivo* half-lives relative to known antibodies such as, *e.g.*, SYNAGIS®. In particular, the present invention encompasses

20 antibodies which immunospecifically bind to one or more RSV antigens and have increased *in vivo* half-lives relative to known antibodies (*e.g.*, SYNAGIS®), said increased half-lives resulting from one or more modifications (*e.g.*, substitutions, deletions, or insertions) in amino acid residues identified to be involved in the interaction of the Fc domain of said antibodies and the FcRn receptor. The present invention also encompasses pegylated

25 antibodies and fragments thereof which immunospecifically bind to one or more RSV antigens and have increased *in vivo* half-lives relative to known antibodies such as, *e.g.*, SYNAGIS®. The increased *in vivo* half-lives of antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens reduce the dosage and/or frequency of administration of said antibodies or fragments thereof to a subject.

30 The invention encompasses sustained release formulations for the administration of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens to a subject. The sustained release formulations reduce the dosage and/or frequency of administration of said antibodies or antibody fragments to a subject. Further, the sustained release formulations may be administered to maintain a therapeutically or

prophylactically effective serum titer which does not exceed a certain maximum serum titer for a certain period of time.

The present invention encompasses methods of delivering one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens directly to the site of RSV infection. In particular, the invention encompasses pulmonary delivery of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens. The improved methods of delivering of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens reduce the dosage and/or frequency of administration of said antibodies or antibody fragments to a subject.

10 The present invention provides antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have an association rate constant or  $k_{on}$  rate (antibody (Ab) + antigen (Ag)  $\xrightarrow{k_{on}} \text{Ab-Ag}$ ) of at least  $10^5 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1} \text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1} \text{s}^{-1}$ . In particular, the present invention provides compositions for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection, said compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have an  $k_{on}$  rate of at least  $10^5 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1} \text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1} \text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1} \text{s}^{-1}$ .

15 The present invention provides antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have a  $k_{off}$  rate (antibody (Ab) + antigen (Ag)  $\xleftarrow{k_{off}} \text{Ab-Ag}$ ) of less than  $10^{-1} \text{ s}^{-1}$ , less than  $5 \times 10^{-1} \text{ s}^{-1}$ , less than  $10^{-2} \text{ s}^{-1}$ , less than  $5 \times 10^{-2} \text{ s}^{-1}$ , less than  $10^{-3} \text{ s}^{-1}$ , less than  $5 \times 10^{-3} \text{ s}^{-1}$ , less than  $10^{-4} \text{ s}^{-1}$ , less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5 \times 10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ , or less than  $10^{-10} \text{ s}^{-1}$ . In particular, the present invention provides compositions for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection, said compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have a  $k_{off}$  rate of less than  $10^{-1} \text{ s}^{-1}$ , less than  $5 \times 10^{-1} \text{ s}^{-1}$ , less than  $10^{-2} \text{ s}^{-1}$ , less than  $5 \times 10^{-2} \text{ s}^{-1}$ , less than  $10^{-3} \text{ s}^{-1}$ , less than  $5 \times 10^{-3} \text{ s}^{-1}$ , less than  $10^{-4} \text{ s}^{-1}$ , less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5 \times 10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ , or less than  $10^{-10} \text{ s}^{-1}$ .

20 The present invention also provides antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have an affinity constant or  $K_a$

( $k_{on}/k_{off}$ ) of at least  $10^2 \text{ M}^{-1}$ , at least  $5 \times 10^2 \text{ M}^{-1}$ , at least  $10^3 \text{ M}^{-1}$ , at least  $5 \times 10^3 \text{ M}^{-1}$ , at least  $10^4 \text{ M}^{-1}$ , at least  $5 \times 10^4 \text{ M}^{-1}$ , at least  $10^5 \text{ M}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}$ , at least  $10^6 \text{ M}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}$ , at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . In particular, the present invention provides compositions for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection, said compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to

one or more RSV antigens and have a  $K_a$  of at least  $10^2 \text{ M}^{-1}$ , at least  $5 \times 10^2 \text{ M}^{-1}$ , at least  $10^3 \text{ M}^{-1}$ , at least  $5 \times 10^3 \text{ M}^{-1}$ , at least  $10^4 \text{ M}^{-1}$ , at least  $5 \times 10^4 \text{ M}^{-1}$ , at least  $10^5 \text{ M}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}$ , at least  $10^6 \text{ M}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}$ , at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ .

The present invention provides antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have a median effective concentration ( $EC_{50}$ ) of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay. In particular, the present invention provides compositions for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection, said compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and have an  $EC_{50}$  of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay.

The present invention also provides antibodies or fragments thereof comprising a VH domain having the amino acid sequence of any VH domain listed in Table 2 and compositions comprising said antibodies or antibody fragments for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. The present invention also provides antibodies or fragments thereof comprising one or more VH complementarity determining regions (CDRs) having the amino acid sequence of one or more VH CDRs listed in Table 2 and/or Table 3 and compositions comprising said

antibodies or antibody fragments for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. The present invention also provides antibodies or fragments thereof comprising a VL domain having the amino acid sequence of any VL domain listed in Table 2. The present invention also provides antibodies or

5 fragments thereof comprising one or more VL CDRs having the amino acid sequence of one or more VL CDRs listed in Table 2 and/or Table 3 and compositions comprising said antibodies or antibody fragments for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. The present invention further provides antibodies comprising a VH domain and a VL domain having the amino acid sequence of

10 any VH domain and VL domain listed in Table 2 and compositions comprising said antibodies or antibody fragments for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. The present invention further provides antibodies comprising one or more VH CDRs and one or more VL CDRs having the amino acid sequence of one or more VH CDRs and one or more VL CDRs listed in Table 2 and/or

15 3 and compositions comprising said antibodies or antibody fragments for use in the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. In the above embodiments, preferably the antibody binds immunospecifically to a RSV antigen.

The present invention also encompasses methods for achieving a serum titer of at

20 least 40  $\mu\text{g/ml}$  of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens in a mammal, preferably a primate and most preferably a human. In particular, the present invention provides methods for achieving a serum titer of at least 40  $\mu\text{g/ml}$  (preferably at least 75  $\mu\text{g/ml}$ , more preferably at least 100  $\mu\text{g/ml}$ , and most preferably at least 150  $\mu\text{g/ml}$ ) of an antibody or fragment thereof that immunospecifically

25 binds to a RSV antigen in a non-primate mammal, comprising administering a dose of less than 2.5 mg/kg (preferably 1.5 mg/kg or less) of the antibody or antibody fragment to the non-primate mammal and measuring the serum titer of the antibody or antibody fragment at least 1 day after administering the dose to the non-primate mammal. The present invention also provides methods for achieving a serum titer of at least 150  $\mu\text{g/ml}$  (preferably at least

30 200  $\mu\text{g/ml}$ ) of an antibody or fragment thereof that immunospecifically binds to a RSV antigen in a non-primate mammal, comprising administering a dose of approximately 5 mg/kg of the antibody or antibody fragment to the non-primate mammal and measuring the serum titer of the antibody or antibody fragment at least 1 day after the administration of the dose to the non-primate mammal.

The present invention also provides methods for achieving a serum titer of at least 40  $\mu\text{g}/\text{ml}$  of an antibody or fragment thereof that immunospecifically binds to a RSV antigen in a primate, comprising administering a first dose of 10  $\text{mg}/\text{kg}$  (preferably 5  $\text{mg}/\text{kg}$  or less and more preferably 1.5  $\text{mg}/\text{kg}$  or less) of the antibody or antibody fragment to the primate and measuring the serum titer of the antibody or antibody fragment 20 days (preferably 25, 30, 35 or 40 days) after administrating the first dose to the primate and prior to the administration of any subsequent dose. The present invention also provides methods for achieving a serum titer of at least 75  $\mu\text{g}/\text{ml}$  (preferably at least 100  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , or at least 200  $\mu\text{g}/\text{ml}$ ) of an antibody or fragment thereof that immunospecifically binds to a RSV antigen in a primate, comprising administering a first dose of approximately 15  $\text{mg}/\text{kg}$  of the antibody or antibody fragment to the primate and measuring the serum titer of the antibody or antibody fragment 20 days (preferably 25, 30, 35 or 40 days) after administering the first dose to the primate but prior to any subsequent dose.

The present invention also provides methods for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a human subject, said methods comprising administering to said human subject at least a first dose of approximately 15  $\text{mg}/\text{kg}$  of an antibody or fragment thereof that immunospecifically binds to a RSV antigen so that said human subject has a serum antibody titer of at least 75  $\mu\text{g}/\text{ml}$ , preferably at least 100  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , or at least 200  $\mu\text{g}/\text{ml}$  30 days after the administration of the first dose of the antibody or antibody fragment and prior to the administration of a subsequent dose. The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a human subject, said methods comprising administering to said human subject at least a first dose of less than 15  $\text{mg}/\text{kg}$  (preferably 10  $\text{mg}/\text{kg}$  or less, more preferably 5  $\text{mg}/\text{kg}$  or less, and most preferably 1.5  $\text{mg}/\text{kg}$  or less) of an antibody or fragment thereof that immunospecifically binds to a RSV antigen so that said human subject has a serum antibody titer of at least 75  $\mu\text{g}/\text{ml}$ , preferably at least 100  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , or at least 200  $\mu\text{g}/\text{ml}$  30 days after the administration of the first dose of the antibody or antibody fragment and prior to the administration of a subsequent dose. The present invention further provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a human subject, said methods comprising administering to said human subject a first dose of an antibody or fragment thereof that immunospecifically binds to a RSV antigen such that a prophylactically or therapeutically effective serum titer of less than 10  $\mu\text{g}/\text{ml}$  is achieved no more than 30 days after administering the antibody or antibody fragment.

The present invention provides methods for achieving a therapeutically or prophylactically effective serum titer in a mammal, said methods comprising administering to said mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has a  $k_{on}$  rate (antibody (Ab) + antigen (Ag)  $\xrightarrow{k_{on}}$  Ab-Ag) of at least  $2.5 \times 10^5 M^{-1} s'$ , preferably at least  $3 \times 10^5 M^{-1} s'$ , at least  $5 \times 10^5 M^{-1} s'$ , at least  $10^6 M^{-1} s'$ , at least  $5 \times 10^6 M^{-1} s'$ , at least  $10^7 M^{-1} s'$ , at least  $5 \times 10^7 M^{-1} s'$  or at least  $10^8 M^{-1} s'$ . In particular, the present invention provides methods for achieving a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than  $30 \mu\text{g/ml}$  (and is preferably at least  $2 \mu\text{g/ml}$ , more preferably at least  $4 \mu\text{g/ml}$ , and most preferably at least  $6 \mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period, comprising administering to a mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has a  $k_{on}$  rate of at least  $2.5 \times 10^5 M^{-1} s'$ , preferably at least  $3 \times 10^5 M^{-1} s'$ , at least  $5 \times 10^5 M^{-1} s'$ , at least  $10^6 M^{-1} s'$ , at least  $5 \times 10^6 M^{-1} s'$ , at least  $10^7 M^{-1} s'$ , at least  $5 \times 10^7 M^{-1} s'$ , or at least  $10^8 M^{-1} s'$ . Preferably, the antibody or antibody fragment has a higher  $k_{on}$  rate than SYNAGIS®.

The present invention also provides methods of neutralizing RSV using an antibody or fragment thereof which immunospecifically bind to a RSV antigen and which has a  $k_{on}$  rate of at least  $2.5 \times 10^5 M^{-1} s'$ , preferably at least  $3 \times 10^5 M^{-1} s'$ , at least  $5 \times 10^5 M^{-1} s'$ , at least  $10^6 M^{-1} s'$ , at least  $5 \times 10^6 M^{-1} s'$ , at least  $10^7 M^{-1} s'$ , at least  $5 \times 10^7 M^{-1} s'$ , or at least  $10^8 M^{-1} s'$  to achieve a prophylactically or therapeutically effective serum titer, wherein said effective serum titer is less than  $30 \mu\text{g/ml}$  (and is preferably at least  $2 \mu\text{g/ml}$ , more preferably at least  $4 \mu\text{g/ml}$ , and most preferably at least  $6 \mu\text{g/ml}$ ) 20, 25, 30, or 35 days after administration without any other dosage administration. Preferably, the antibody or antibody fragment has a higher  $k_{on}$  rate than SYNAGIS®.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering to said mammal, a dose of less than  $15 \text{ mg/kg}$  (preferably  $5 \text{ mg/kg}$  or less, more preferably  $3 \text{ mg/kg}$  or less, and most preferably  $1.5 \text{ mg/kg}$  or less) of an antibody or fragment thereof which immunospecifically binds to a RSV antigen and has a  $k_{on}$  rate of at least  $2.5 \times 10^5 M^{-1} s'$ , preferably at least  $3 \times 10^5 M^{-1} s'$ , at least  $5 \times 10^5 M^{-1} s'$ , at least  $10^6 M^{-1} s'$ , at least  $5 \times 10^6 M^{-1} s'$ , at least  $10^7 M^{-1} s'$ , at least  $5 \times 10^7 M^{-1} s'$ , or at least  $10^8 M^{-1} s'$ . Preferably, the antibody or antibody fragment has a higher  $k_{on}$  rate for the RSV F glycoprotein than SYNAGIS®.

The present invention also provides methods for achieving a therapeutically or prophylactically effective serum titer in a mammal, said methods comprising administering to said mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has a  $K_{off}$  rate (antibody (Ab) + antigen (Ag)  $\xleftarrow{K_{off}}$  Ab - Ag) of less than  $6.5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $3 \times 10^{-4} \text{ sec}^{-1}$ , less than  $2 \times 10^{-4} \text{ sec}^{-1}$ , less than  $1 \times 10^{-4} \text{ sec}^{-1}$ , or less than  $5 \times 10^{-3} \text{ sec}^{-1}$ . In particular, the present invention provides methods for achieving a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period, comprising administering to a mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has a  $K_{off}$  rate of less than  $6.5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $3 \times 10^{-4} \text{ sec}^{-1}$ , less than  $2 \times 10^{-4} \text{ sec}^{-1}$ , less than  $1 \times 10^{-4} \text{ sec}^{-1}$ , or less than  $3 \times 10^{-3} \text{ sec}^{-1}$ . Preferably, the antibody or fragment thereof has a lower  $K_{off}$  rate than SYNAGIS®.

The present invention also provides methods of neutralizing RSV using an antibody or antibody fragment thereof which immunospecifically binds to a RSV antigen and which has a  $K_{off}$  rate of less than  $6.5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $3 \times 10^{-4} \text{ sec}^{-1}$ , less than  $2 \times 10^{-4} \text{ sec}^{-1}$ , less than  $1 \times 10^{-4} \text{ sec}^{-1}$ , or less than  $5 \times 10^{-3} \text{ sec}^{-1}$  to achieve a prophylactically or therapeutically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) 20, 25, 30, or 35 days after administration without any other dosage administration. Preferably, the antibody or antibody fragment has a lower  $K_{off}$  than SYNAGIS®.

The present invention also provides methods for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering to a said mammal a dose of less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of an antibody or a fragment thereof which immunospecifically binds to a RSV antigen and which has a  $K_{off}$  rate of less than  $6.5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $5 \times 10^{-4} \text{ sec}^{-1}$ , less than  $3 \times 10^{-4} \text{ sec}^{-1}$ , less than  $2 \times 10^{-4} \text{ sec}^{-1}$ , less than  $1 \times 10^{-4} \text{ sec}^{-1}$ , or less than  $5 \times 10^{-3} \text{ sec}^{-1}$ . Preferably, the antibody or antibody fragment has a lower  $K_{off}$  rate than SYNAGIS®.

The present invention also provides methods for achieving a therapeutically or prophylactically effective serum titer in a mammal, said methods comprising administering

to said mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has an EC<sub>50</sub> of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay. In particular, the present invention provides methods for achieving a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30 µg/ml (and is preferably at least 2 µg/ml, more preferably at least 4 µg/ml, and most preferably at least 6 µg/ml) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period,

comprising administering to a mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has an EC<sub>50</sub> of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay. Preferably, the antibody or antibody fragment has a lower EC<sub>50</sub> than SYNAGIS®.

The present invention also provides methods of neutralizing RSV using an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has an EC<sub>50</sub> of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay to achieve a prophylactically or therapeutically effective serum titer, wherein said effective serum titer is less than 30 µg/ml (and is preferably at least 2 µg/ml, more preferably at least 4 µg/ml, and most preferably at least 6 µg/ml) 20, 25, 30, or 35 days after administration without any other dosage administration. Preferably, the antibody or antibody fragment has a lower EC<sub>50</sub> than SYNAGIS®.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering to said mammal a dose of less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of an antibody or a fragment thereof which immunospecifically binds to a RSV antigen and which has an EC<sub>50</sub> of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay. Preferably, the antibody or antibody fragment has a lower EC<sub>50</sub> than SYNAGIS®.

The present invention provides methods for achieving a therapeutically or prophylactically effective serum titer in a mammal, said methods comprising administering to said mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen and which has an affinity constant ( $K_a$ ) for a RSV antigen of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . In particular, the present invention also provides methods for achieving a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period, comprising administering to a mammal an antibody or fragment thereof that has an affinity constant ( $K_a$ ) for a RSV antigen of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . Preferably, the antibody or antibody fragment has a higher affinity for a RSV F glycoprotein than SYNAGIS®.

20 The present invention also provides methods of achieving a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period, comprising administering to a mammal an antibody or fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity than known antibodies such as, *e.g.*, SYNAGIS®.

25 The present invention also provides methods of neutralizing RSV using an antibody or fragment thereof that has an affinity constant ( $K_a$ ) for a RSV antigen of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  to achieve a prophylactically or therapeutically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is at least 2  $\mu\text{g/ml}$  and more preferably at least 6  $\mu\text{g/ml}$ ) 20, 25, 30, or 35 days after administration

without any other dosage administration. Preferably, the antibody or antibody fragment has a higher affinity for the RSV F glycoprotein than SYNAGIS®. The present invention also provides methods of neutralizing RSV using an antibody or fragment thereof that has a higher avidity than known antibodies such as, e.g., SYNAGIS®.

- 5 The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering to said mammal a dose of less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of an antibody or fragment thereof that has an affinity constant ( $K_a$ ) for a RSV antigen of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . Preferably, the antibody or antibody fragment has a higher affinity for the RSV F glycoprotein than SYNAGIS®.
- 10 15 The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering to said mammal a first dose of less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of an antibody or fragment thereof that has a higher avidity than known antibodies such as, e.g., SYNAGIS®.
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The present invention encompasses methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, comprising administering to said mammal a first dose of a prophylactically or therapeutically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, e.g., SYNAGIS®, wherein said effective amount is less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of said antibodies or antibody fragments which dose results in a serum titer of less than 30  $\mu\text{g/ml}$  (which is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) at least 20 days (preferably at least 25, at least 30, or at least 35 days) after the administration of the first dose and prior to the administration of a subsequent dose. In particular, the present invention provides methods for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a human subject, comprising administering to said human subject a first dose of less than 5 mg/kg (preferably 3 mg/kg or less, and most preferably 1.5 mg/kg) of an

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antibody or fragment thereof that immunospecifically binds to a RSV antigen with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11}$

5  $\text{M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$ ) so that said human subject has a serum antibody titer of less than 30  $\mu\text{g/ml}$  (which is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) at least 20 days (preferably at least 25, at least 30, or at least 35 days) after the administration of the first dose of the antibody or antibody fragment and prior to the administration of a subsequent dose.

10 The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or fragments thereof comprising a VH domain having an amino acid sequence of any VH domain listed in Table 2 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a

15 mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or fragments thereof comprising one or more VH complementarity determining regions (CDRs) having the amino acid sequence of one or more VH CDRs listed in Table 2 and/or Table 3 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. Preferably, said antibodies or antibody fragments immunospecifically bind to a RSV antigen.

The present invention also provides methods for preventing, treating or ameliorating

30 one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or fragments thereof comprising a VL domain having the amino acid sequence of any VL domain listed in Table 2 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g/ml}$  (and is preferably at least 2  $\mu\text{g/ml}$ , more preferably at least 4  $\mu\text{g/ml}$ , and most preferably at least 6  $\mu\text{g/ml}$ ) after a certain

number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or 5 more antibodies or fragments thereof comprising one or more VL CDRs having the amino acid sequence of one or more VL CDRs listed in Table 2 and/or Table 3 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain number of days (for example, but not 10 limited to, 20, 25, 30 or 35 days) without any other dosing within that period. Preferably, said antibodies or antibody fragments immunospecifically bind to a RSV antigen.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or 15 fragments thereof comprising a VH domain and a VL domain having the amino acid sequence of any VH domain and VL domain listed in Table 2 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain number of days (for example, but not limited to, 20 20, 25, 30 or 35 days) without any other dosing within that period. The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or fragments thereof comprising one or more VH CDRs and one or more VL CDRs having the amino acid sequence of one or more 25 VH CDRs and one or more VL CDRs listed in Table 2 and/or 3 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. Preferably, said 30 antibodies or antibody fragments immunospecifically bind to a RSV antigen.

In a specific embodiment, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or fragments thereof comprising a VH domain having an amino acid 35 sequence of SEQ ID NO:7, 9, 17, 24, 28, 33, 36, 40, 44, 48, 51, 67, or 78 and/or a VL

domain having an amino acid sequence of SEQ ID NO:8, 11, 13, 21, 26, 30, 34, 38, 42, 46, 49, 52, 54, 56, 58, 60, 62, 64, 65, 68, 70, 71, 74 or 76 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most

5 preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. In a preferred embodiment, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose of one or more antibodies or

10 fragments thereof comprising a VH domain having an amino acid sequence of SEQ ID NO:9, 17, 24, 28, 33, 36, 40, 44, 48, 51, 55, 67 or 78 and/or a VL domain having an amino acid sequence of SEQ ID NO:13, 21, 26, 30, 34, 38, 42, 46, 49, 52, 54, 56, 58, 60, 62, 64, 65, 68, 70, 71, 74 or 76 to achieve a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ ,

15 more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period. In another embodiment, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said methods comprising administering to said mammal a first dose

20 of one or more antibodies or fragments thereof comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, 12, 20, 29, or 79 and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, 16 or 61 to a therapeutically or prophylactically effective serum titer, wherein said effective serum titer is less than 30  $\mu\text{g}/\text{ml}$  (and is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) after a certain

25 number of days (for example, but not limited to, 20, 25, 30 or 35 days) without any other dosing within that period.

The present invention also provides compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and which have increased *in vivo* half-lives compared to known anti-RSV antibodies as a result of, *e.g.*, one or more modifications in amino acid residues identified to be involved in the interaction between the Fc domain of said antibodies or antibody fragments and the FcRn receptor. In one embodiment, a composition of the invention comprises HL-SYNAGIS or an antigen-binding fragment thereof. In another embodiment, a composition of the invention comprises one or more antibodies or fragments thereof

30 which immunospecifically bind to one or more RSV antigens with a higher avidity and/or a

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higher affinity than known antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen) and which comprise an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS®. In accordance with this embodiment, the increased affinity of the Fc domain of said antibodies or antibody fragments results in an *in vivo* half-life of said antibodies or antibody fragments of at least 25 days, preferably at least 30 days, more preferably at least 30 days, and most preferably at least 40 days. In another embodiment, a composition of the invention comprises HL-SYNAGIS or an antigen-binding fragment thereof and one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and which comprise an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS®.

The present invention also provides compositions comprising one or more pegylated antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens. In one embodiment, a composition of the invention comprises pegylated SYNAGIS® or a fragment thereof. In another embodiment, a composition of the invention comprises one or more pegylated antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS®. In yet another embodiment, a composition of the invention comprises pegylated SYNAGIS® or an antigen-binding fragment thereof and one or more pegylated antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS®.

The present invention also provides compositions comprising one or more pegylated antibodies or fragments thereof which comprise an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS®. In one embodiment, a composition of the invention comprises a pegylated HL-SYNAGIS or an antigen-binding fragment thereof. In another embodiment, a composition of the invention comprises one or more pegylated antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with a higher avidity and/or a higher affinity than known such as, *e.g.*, SYNAGIS® and which comprise an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS®.

The present invention encompasses methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human,

comprising administering to said mammal a first dose of a prophylactically or therapeutically effective amount of HL-SYNAGIS or an antigen-binding fragment thereof, wherein said effective amount is approximately 15 mg/kg of said antibodies or fragments thereof which dose results in a serum titer of at least 30  $\mu$ g/ml at least 30 days after the

5 administration of the first dose and prior to the administration of a subsequent dose. In particular, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a human subject, comprising administering to said human subject a first dose of 15 mg/kg of HL-SYNAGIS or an antigen-binding fragment thereof so that said human subject has a serum antibody titer of at

10 least 30  $\mu$ g/ml at least 30 days after the administration of the first dose of the antibody or antibody fragment and prior to the administration of a subsequent dose.

The present invention also encompasses methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, comprising administering to said mammal a first dose of a

15 prophylactically or therapeutically effective amount of one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at

20 least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen), wherein said effective amount is less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of said antibodies or fragments thereof which dose results in a serum titer of less than 30  $\mu$ g/ml (which is preferably at least 2  $\mu$ g/ml, more preferably at least 4  $\mu$ g/ml,

25 and most preferably at least 6  $\mu$ g/ml) at least 20 days (preferably at least 25, at least 30, or at least 35 days) after the administration of the first dose and prior to the administration of a subsequent dose. In particular, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a human subject, comprising administering to said human subject a first dose of less than 5 mg/kg

30 (preferably 1.5 mg/kg or less) of an antibody or a fragment thereof which has an increased *in vivo* half-life and which immunospecifically binds to a RSV antigen with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at

35 least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV

antigen) so that said human subject has a serum antibody titer of less than 30  $\mu\text{g}/\text{ml}$  (which is preferably at least 2  $\mu\text{g}/\text{ml}$ , more preferably at least 4  $\mu\text{g}/\text{ml}$ , and most preferably at least 6  $\mu\text{g}/\text{ml}$ ) at least 25 days (preferably at least 30, at least 35, or at least 40 days) after the administration of the first dose of the antibody or antibody fragment and prior to the 5 administration of a subsequent dose.

The present invention provides sustained release formulations comprising one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens. In one embodiment, a sustained release formulation comprises SYNAGIS® or a fragment thereof. In another embodiment, a sustained release formulation comprises one or 10 more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 15$  15  $10^{12} \text{ M}^{-1}$  for a RSV antigen). In another embodiment, a sustained release formulation comprises SYNAGIS® or an antigen-binding fragment thereof and one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , 20 at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen). In another embodiment, HL-SYNAGIS or an antigen-binding fragment thereof is formulated in as sustained release formulation. In yet another embodiment, antibodies or fragments thereof which have higher avidity and/or higher affinity for one or more RSV 25 antigens than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen) and which 30 comprises an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS® are formulated in sustained release formulations.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, comprising administering to said mammal a first dose of a prophylactically or therapeutically effective amount of one or more antibodies or fragments thereof that 35 immunospecifically bind to one or more RSV antigens in a sustained release formulation,

wherein said effective amount is a dose of 15 mg/kg or less of said antibodies or fragments thereof, which dose, preferably results in a serum titer of at least 2  $\mu$ g/ml (preferably at least 5  $\mu$ g/ml, at least 10  $\mu$ g/ml, at least 20  $\mu$ g/ml, at least 30  $\mu$ g/ml, or at least 40  $\mu$ g/ml) for at least 20 days (preferably at least 25, 30, 35 or 40 days) after the administration of the first 5 dose and prior to the administration of a subsequent dose.

In one embodiment, a mammal, preferably a human, is administered a first dose of a prophylactically or therapeutically effective amount of SYNAGIS® or an antigen-binding fragment thereof in a sustained release formulation, wherein said effective amount is a dose of approximately 15 mg/kg of SYNAGIS® or an antigen-binding fragment thereof which 10 dose results in a serum titer of at least 20  $\mu$ g/ml (preferably at least 30  $\mu$ g/ml, more preferably at least 40  $\mu$ g/ml, and most preferably at least 50  $\mu$ g/ml) for at least 30 days (preferably at least 35 days, more preferably at least 40 days, and most preferably at least 45 days) after the administration of the first dose and prior to the administration of a subsequent dose. In a preferred embodiment, a mammal, preferably a human, is 15 administered a first dose of a prophylactically or therapeutically effective amount of SYNAGIS® or an antigen-binding fragment thereof in a sustained release formulation, wherein said effective amount is a dose of 15 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof which dose results in a serum titer of 20  $\mu$ g/ml (preferably at least 30  $\mu$ g/ml, more preferably at least 40  $\mu$ g/ml, and most preferably at least 50  $\mu$ g/ml) at least 20 30 days (preferably at least 35 days, more preferably at least 40 days, and most preferably at least 45 days) after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a prophylactically or therapeutically effective amount of one or more antibodies or 25 fragments thereof which immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV 30 antigen) in a sustained release formulation, wherein said effective amount is a dose of less than 15 mg/kg (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of said antibodies or antibody fragments which dose results in a serum titer of less than 30  $\mu$ g/ml (which is preferably at least 2  $\mu$ g/ml, more preferably at least 4  $\mu$ g/ml, and most preferably at least 6  $\mu$ g/ml) for at least 20 days (preferably at least 35, at least 30, at least 35, or at least 40 days) after the administration of the first dose and 35 25, at least 30, at least 35, or at least 40 days) after the administration of the first dose and

prior to the administration of a subsequent dose. In a preferred embodiment, a mammal, preferably a human, is administered a first dose of a prophylactically or therapeutically effective amount of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known

5 antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen) in a sustained release formulation, wherein said effective amount is a dose of less than 15 mg/kg of said antibodies or antibody

10 fragments which dose results in a serum titer of 10  $\mu\text{g/ml}$  for at least 20 days (preferably at least 25, at least 30, at least 35 or at least 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. In accordance with this embodiment, the prophylactically or therapeutically effective amount of the dose of the antibodies or antibody fragments is approximately 0.5 mg/kg, preferably 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5

15 mg/kg, 7.5 mg/kg, 10 mg/kg, 12 mg/kg, or 14 mg/kg. In another preferred embodiment, a mammal, preferably a human, is administered a first dose of a prophylactically or therapeutically effective amount of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher avidity and/or higher affinity than known antibodies such as, *e.g.*, SYNAGIS® (*e.g.*, antibodies or antibody

20 fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV antigen) in a sustained release formulation, wherein said effective amount is a dose of 1.5 mg/kg of said antibodies or antibody fragments which dose results in a serum titer of 10  $\mu\text{g/ml}$  for at least 20 days

25 (preferably at least 25, at least 30, at least 35, or at least 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

Additionally, the present invention provides sustained release compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens, which sustained release compositions maintain a certain serum titer in a subject for a certain period of time without exceeding a particular serum titer. In one embodiment, a sustained release formulation comprising SYNAGIS® or an antigen-binding fragment thereof maintains a serum titer in a mammal, preferably a human, of approximately 25  $\mu\text{g/ml}$  (preferably 30  $\mu\text{g/ml}$ , more preferably 40  $\mu\text{g/ml}$ , and most preferably 50  $\mu\text{g/ml}$ ) without exceeding a serum titer of approximately 100  $\mu\text{g/ml}$

30 (preferably 75  $\mu\text{g/ml}$ ) for at least 20 days (preferably at least 25, 30, 35, or 40 days). In

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another embodiment, a sustained release formulation comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with a higher avidity and/or a higher affinity than previously known antibodies such as, e.g., SYNAGIS®, maintains a serum titer in a mammal, preferably a human, of approximately 2  $\mu\text{g}/\text{ml}$  (preferably 6  $\mu\text{g}/\text{ml}$ , 10  $\mu\text{g}/\text{ml}$ , 20  $\mu\text{g}/\text{ml}$ , or 30  $\mu\text{g}/\text{ml}$ ) without exceeding a serum titer of approximately 40  $\mu\text{g}/\text{ml}$  (preferably 75  $\mu\text{g}/\text{ml}$ ) for at least 20 days (preferably at least 25, 30, 35, or 40 days).

The present invention encompasses methods of preventing, treating or ameliorating one or more symptoms of RSV infection in a mammal, preferably a human, by 10 administering sustained release formulations of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens and which have increased *in vivo* half-lives. In one embodiment, a sustained release formulation comprising HL-SYNAGIS or an antigen-binding fragment thereof is administered to a mammal, preferably a human, to prevent, treat, or ameliorate one or more symptoms associated with a RSV 15 infection. In another embodiment, a sustained release formulation comprising one or more antibodies or fragments thereof which have higher avidity and/or higher affinity for one or more RSV antigens than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for a RSV 20 antigen) and which comprises an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS® are administered to a mammal, preferably a human, to prevent, treat, or ameliorate one or more symptoms associated with a RSV infection.

25 The present invention also provides pulmonary delivery systems for administering one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens. In particular, the present invention provides compositions for pulmonary delivery, said compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens. SYNAGIS® or an antigen-binding 30 fragment thereof can be incorporated into compositions for pulmonary delivery. HL-SYNAGIS or an antigen-binding fragment thereof can be incorporated into compositions for pulmonary delivery. One or more antibodies or fragments thereof that bind to one or more RSV antigens with higher affinity and/or higher avidity than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at

least  $10^{10}$  M<sup>-1</sup>, at least  $5 \times 10^{10}$  M<sup>-1</sup>, at least  $10^{11}$  M<sup>-1</sup>, at least  $5 \times 10^{11}$  M<sup>-1</sup>, at least  $10^{12}$  M<sup>-1</sup>, or at least  $5 \times 10^{12}$  M<sup>-1</sup> for a RSV antigen) can be incorporated into compositions for pulmonary delivery. Further, one or more antibodies or fragments thereof which bind to one or more RSV antigens with higher affinity and/or higher avidity than known antibodies

5 such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments with an affinity of at least  $2 \times 10^8$  M<sup>-1</sup>, at least  $2.5 \times 10^8$  M<sup>-1</sup>, at least  $5 \times 10^8$  M<sup>-1</sup>, at least  $10^9$  M<sup>-1</sup>, at least  $5 \times 10^9$  M<sup>-1</sup>, at least  $10^{10}$  M<sup>-1</sup>, at least  $5 \times 10^{10}$  M<sup>-1</sup>, at least  $10^{11}$  M<sup>-1</sup>, at least  $5 \times 10^{11}$  M<sup>-1</sup>, at least  $10^{12}$  M<sup>-1</sup>, or at least  $5 \times 10^{12}$  M<sup>-1</sup> for a RSV antigen) and which comprise an Fc domain with increased affinity for the FcRn receptor relative to the Fc domain of SYNAGIS® can be incorporated

10 into compositions for pulmonary delivery.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection, said methods comprising administering to a mammal, preferably a human, a composition for pulmonary delivery comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens. In particular, the present invention provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection, said methods comprising administering to a mammal, preferably a human, a composition for pulmonary delivery comprising SYNAGIS® or fragments thereof. The present invention also provides methods for preventing, treating or ameliorating one or more symptoms associated with a RSV infection, said methods comprising administering to a mammal, preferably a human, a composition for pulmonary delivery comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than known antibodies such as, e.g., SYNAGIS® (e.g., antibodies or antibody fragments having an affinity of at least  $2 \times 10^8$  M<sup>-1</sup>, at least  $2.5 \times 10^8$  M<sup>-1</sup>, at least  $5 \times 10^8$  M<sup>-1</sup>, at least  $10^9$  M<sup>-1</sup>, at least  $5 \times 10^9$  M<sup>-1</sup>, at least  $10^{10}$  M<sup>-1</sup>, at least  $5 \times 10^{10}$  M<sup>-1</sup>, at least  $10^{11}$  M<sup>-1</sup>, at least  $5 \times 10^{11}$  M<sup>-1</sup>, at least  $10^{12}$  M<sup>-1</sup>, or at least  $5 \times 10^{12}$  M<sup>-1</sup> for one or more RSV antigens).

In one embodiment, a first dose of a prophylactically or therapeutically effective amount of a composition comprising SYNAGIS® or an antigen-binding fragment thereof is administered to the lungs of a mammal, preferably a human, and results in an antibody concentration of at least 20 ng per mg of lung protein (preferably at least 40 ng/mg, at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg) at least 20 days (preferably at least 25, 30, 35 or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

35 Preferably, the prophylactically or therapeutically effective amount is a dose of

approximately 0.01 mg/kg, (preferably at least 0.1 mg/kg, at least 1 mg/kg, at least 2 mg/kg, at least 4 mg/kg, at least 5 mg/kg or at least 10 mg/kg) of SYNAGIS® or an antigen-binding fragment thereof.

In another embodiment, a first dose of a prophylactically or therapeutically effective amount of a composition comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than known antibodies such as, e.g., SYNAGIS®, (e.g., antibodies or antibody fragments having an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $5 \times 10^{12} \text{ M}^{-1}$  for one or more RSV antigens) is administered to the lungs of a mammal, preferably a human and results in an antibody concentration of 20 ng per mg of lung protein (preferably at least 40 ng/mg, at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg), at least 200 ng/mg, at least 250 ng/mg, at least 500 ng/mg, at least 750 ng/mg, at least 1  $\mu\text{g}/\text{mg}$ , at least 2  $\mu\text{g}/\text{mg}$ , at least 5  $\mu\text{g}/\text{mg}$ , at least 10  $\mu\text{g}/\text{mg}$ , at least 15  $\mu\text{g}/\text{mg}$ , or at least 25  $\mu\text{g}/\text{mg}$ ) at least 20 days (preferably at least 25, 30, 35 or 40 days) at least 20 days (preferably at least 25, at least 30, at least 35 or at least 40 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the prophylactically effective amount is a dose of approximately 0.001 mg/kg, (preferably at least 0.005 mg/kg, at least 0.01 mg/kg, at least 0.05 mg/kg, at least 0.1 mg/kg, at least 1 mg/kg, at least 2 mg/kg, at least 4 mg/kg, at least 5 mg/kg or at least 10 mg/kg) of said antibodies or antibody fragments.

The present invention further provides detectable or diagnostic compositions comprising using antibodies or fragments thereof that immunospecifically bind to a RSV antigen, and methods for detecting or diagnosing a RSV infection utilizing said compositions.

### 3.1. DEFINITIONS

The term "analog" as used herein refers to a polypeptide that possesses a similar or identical function as a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment but does not necessarily comprise a similar or identical amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment, or possess a similar or identical structure of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment. A polypeptide that has a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a

polypeptide having an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment described herein; (b) a polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment described herein of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the nucleotide sequence encoding a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment described herein. A polypeptide with similar structure to a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a RSV polypeptide, a fragment of a RSV, an antibody, or antibody fragment described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

The term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody that immunospecifically binds to a RSV polypeptide, or an antibody fragment that immunospecifically binds to a RSV polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a RSV polypeptide, a fragment of a RSV polypeptide, an antibody that immunospecifically binds to a RSV polypeptide, or an antibody fragment that immunospecifically binds to a RSV polypeptide which has been modified, *i.e.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment may be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups,

proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a RSV polypeptide, a fragment of a RSV polypeptide, an antibody, or antibody fragment described herein.

10        The term "effective neutralizing titer" as used herein refers to the amount of antibody which corresponds to the amount present in the serum of animals (human or cotton rat) that has been shown to be either clinically efficacious (in humans) or to reduce virus by 99% in, for example, cotton rats. The 99% reduction is defined by a specific challenge of, e.g.,  $10^3$  pfu,  $10^4$  pfu,  $10^5$  pfu,  $10^6$  pfu,  $10^7$  pfu,  $10^8$  pfu, or  $10^9$  pfu) of RSV.

15        The term "epitopes" as used herein refers to portions of a RSV polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. An epitope having immunogenic activity is a portion of a RSV polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a RSV polypeptide to which an antibody immunospecifically binds as determined by any method well known in the art, for example, by the immunoassays described herein.

20        Antigenic epitopes need not necessarily be immunogenic.

The term "fragment" as used herein refers to a peptide or polypeptide comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino acid residues, at least 70 contiguous amino acid residues, at least 80 amino acid residues, at least contiguous 90 amino acid residues, at least contiguous 100 amino acid residues, at least contiguous 125 amino acid residues, at least 150 contiguous amino acid residues, at least contiguous 175 amino acid residues, at least contiguous 200 amino acid residues, or at least contiguous 250 amino acid residues of the amino acid sequence of a RSV polypeptide or an antibody that immunospecifically binds to a RSV polypeptide.

The term "human infant" as used herein refers to a human less than 24 months, preferably less than 16 months, less than 12 months, less than 6 months, less than 3 months, 35 less than 2 months, or less than 1 month of age.

The term "human infant born prematurely" as used herein refers to a human born at less than 40 weeks gestational age, preferably less than 35 weeks gestational age, who is less than 6 months old, preferably less than 3 months old, more preferably less than 2 months old, and most preferably less than 1 month old.

5 An "isolated" or "purified" antibody or fragment thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody or antibody fragment in which the antibody or antibody

10 fragment is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody or antibody fragment that is substantially free of cellular material includes preparations of antibody or antibody fragment having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the antibody or antibody fragment is

15 recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody or antibody fragment is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the.

20 protein. Accordingly such preparations of the antibody or antibody fragment have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody or antibody fragment of interest. In a preferred embodiment, antibodies of the invention or fragments thereof are isolated or purified.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule.

25 Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a preferred embodiment, nucleic acid molecules encoding

30 antibodies of the invention or fragments thereof are isolated or purified.

The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody or fragment thereof and an amino acid sequence of a heterologous polypeptide (*e.g.*, a non-anti-RSV antigen antibody).

The term "high potency" as used herein refers to antibodies or fragments thereof that

35 exhibit high potency as determined in various assays for biological activity (*e.g.*,

neutralization of RSV) such as those described herein. For example, high potency antibodies of the present invention or fragments thereof have an EC<sub>50</sub> value less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 5 1.75 nM, or less than 2 nM as measured by a microneutralization assay described herein. Further, high potency antibodies of the present invention or fragments thereof result in at least a 75%, preferably at least a 95% and more preferably a 99% lower RSV titer in a cotton rat 5 days after challenge with 10<sup>5</sup> pfu relative to a cotton rat not administered said antibodies or antibody fragments. In certain embodiments of the invention, high potency 10 antibodies of the present invention or fragments thereof exhibit a high affinity and/or high avidity for one or more RSV antigens (e.g., antibodies or antibody fragments having an affinity of at least 2X10<sup>8</sup> M<sup>-1</sup>, at least 2.5X10<sup>8</sup> M<sup>-1</sup>, at least 5X10<sup>8</sup> M<sup>-1</sup>, at least 10<sup>9</sup> M<sup>-1</sup>, at least 5 X 10<sup>9</sup> M<sup>-1</sup>, at least 10<sup>10</sup> M<sup>-1</sup>, at least 5 X 10<sup>10</sup> M<sup>-1</sup>, at least 10<sup>11</sup> M<sup>-1</sup>, at least 5 X 10<sup>11</sup> M<sup>-1</sup>, at least 10<sup>12</sup> M<sup>-1</sup>, or at least 5 X 10<sup>12</sup> M<sup>-1</sup> for one or more RSV antigens).

15 The term "host" as used herein refers to a mammal, preferably a human. The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding 20 generations or integration of the nucleic acid molecule into the host cell genome.

In certain embodiments of the invention, a "prophylactically effective serum titer" is the serum titer in a mammal, preferably a human, that reduces the incidence of a RSV infection in said mammal. Preferably, the prophylactically effective serum titer reduces the incidence of RSV infections in humans with the greatest probability of complications 25 resulting from RSV infection (e.g., a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, a human who has had a bone marrow transplant, a human infant, or an elderly human). In certain other embodiments of the invention, a "prophylactically effective serum titer" is the serum titer in a cotton rat that results in a RSV titer 5 days after challenge 30 with 10<sup>5</sup> pfu that is 99% lower than the RSV titer 5 days after challenge with 10<sup>5</sup> pfu of RSV in a cotton rat not administered an antibody or antibody fragment that immunospecifically binds to a RSV antigen.

In certain embodiments of the invention, a "therapeutically effective serum titer" is the serum titer in a mammal, preferably a human, that reduces the severity, the duration 35 and/or the symptoms associated with a RSV infection in said mammal. Preferably, the

therapeutically effective serum titer reduces the severity, the duration and/or the number symptoms associated with RSV infections in humans with the greatest probability of complications resulting from a RSV infection (e.g., a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or 5 acquired immunodeficiency, a human who has had a bone marrow transplant, a human infant, or an elderly human). In certain other embodiments of the invention, a “therapeutically effective serum titer” is the serum titer in a cotton rat that results in a RSV titer 5 days after challenge with  $10^5$  pfu that is 99% lower than the RSV titer 5 days after challenge with  $10^5$  pfu of RSV in a cotton rat not administered an antibody or antibody 10 fragment that immunospecifically binds to a RSV antigen.

As used herein, “HL-SYNAGIS” is SYNAGIS® with one or more modifications in amino acid residues identified to be involved in the interaction between the Fc domain of SYNAGIS® and the FcRn receptor which results in an increase in the *in vivo* half-life of SYNAGIS® to greater than 21 days. An antigen-binding fragment of HL-SYNAGIS is a 15 fragment of SYNAGIS® which immunospecifically binds to RSV F glycoprotein and has one or more modifications in amino acid residues identified to be involved in the interaction between the Fc domain of SYNAGIS® and the FcRn receptor, wherein said modifications result in an increase in the *in vivo* half-life of the antigen-binding fragment. In accordance with the invention, HL-SYNAGIS or an antigen-binding fragment thereof has an *in vivo* 20 half-life of at least 25 days, preferably at least 30 days, more preferably at least 35 days, and most preferably at least 40 days.

The term “RSV antigen” refers to a RSV polypeptide or fragment thereof to which an antibody or antibody fragment immunospecifically binds. An RSV antigen also refers to an analog or derivative of a RSV polypeptide or fragment thereof to which an antibody or 25 antibody fragment immunospecifically binds.

The term “serum titer” as used herein refers to an average serum titer in a population of least 10, preferably at least 20, and most preferably at least 40 subjects.

The term “antibodies or fragments that immunospecifically bind to a RSV antigen” as used herein refers to antibodies or fragments thereof that specifically bind to a RSV 30 polypeptide or a fragment of a RSV polypeptide and do not non-specifically bind to other polypeptides. Antibodies or fragments that immunospecifically bind to a RSV polypeptide or fragment thereof may have cross-reactivity with other antigens. Preferably, antibodies or fragments that immunospecifically bind to a RSV polypeptide or fragment thereof do not cross-react with other antigens. Antibodies or fragments that immunospecifically bind to a

RSV polypeptide can be identified, for example, by immunoassays or other techniques known to those of skill in the art.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be 5 introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the 10 molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can also be 15 accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264-2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. 20 Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, e.g., for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches can be performed with the XBLAST program parameters set, e.g., to score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule of the 25 present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389-3402. Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., of XBLAST 30 and NBLAST) can be used (see, e.g., <http://www.ncbi.nlm.nih.gov>). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid 35

sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent  
5 identity, typically only exact matches are counted.

#### 4. DESCRIPTION OF THE FIGURES

Figures 1A-1B show the amino acid sequences of the (A) light chain variable region and (B) heavy chain variable region of a high affinity monoclonal antibody that binds to a  
10 RSV antigen the potency of which can be increased by methods described herein or in Applicants' copending applications Serial Nos. 60/168,426 and 60/186,252. For reference purposes, this is the amino acid sequence of the SYNAGIS® antibody disclosed in Johnson et al, 1997, J. Infect. Dis. 176:1215-1224 and U.S. Patent No. 5,824,307. Here, the CDR regions are underlined while non-underlined residues form the framework regions of the  
15 variable regions of each antibody. In this antibody, the CDRs are derived from a mouse antibody while the framework regions are derived from a human antibody. The constant regions (not shown) are also derived from a human antibody.

Figures 2A-2B show the (A) light chain variable region and (B) heavy light chain variable region for an antibody sequence. CDR regions are underlined. This sequence  
20 differs from the sequence disclosed in Figures 1A-1B in the first 4 residues of VH CDR1 of the light chain, residue 103 of the light chain and residue 112 of the heavy chain.

#### 5. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods of preventing, neutralizing, treating and  
25 ameliorating one or more symptoms associated with a RSV infection in a subject comprising administering to said subject one or more antibodies which immunospecifically bind to one or more RSV antigens with high affinity and/or high avidity and/or have a longer serum half-life. The high affinity and/or high avidity of the antibodies of the invention enable the use of lower doses of said antibodies than previously thought to be  
30 effective for the prevention, neutralization, treatment and the amelioration of symptoms associated with RSV infection. The use of lower doses of antibodies which immunospecifically bind to one or more RSV antigens reduces the likelihood of adverse effects, as well as providing a more effective prophylaxis. Further, the high affinity and/or high avidity of the antibodies of the invention enable less frequent administration of said

antibodies than previously thought to be necessary for the prevention, neutralization, treatment and the amelioration of symptoms associated with RSV infection.

The present invention also provides methods of preventing, neutralizing, treating and ameliorating one or more symptoms associated with a RSV infection in a subject

5 comprising administering to said subject one or more antibodies which immunospecifically bind to one or more RSV antigens, said antibodies having a longer half-life than other previously known antibodies.

The present invention also provides improved methods of administering one or more antibodies which immunospecifically bind to one or more RSV antigens to a subject, said

10 methods enable lower doses of said antibodies to be administered to the subject while achieving serum titers effective for the prevention, neutralization, treatment and amelioration of one or more symptoms associated with RSV infection. The present invention encompasses methods of delivering one or more antibodies which immunospecifically bind to one or more RSV antigens directly to the site of RSV infection.

15 In particular, the invention encompasses pulmonary delivery of one or more antibodies which immunospecifically bind to one or more RSV antigens. The improved methods of delivering of one or more antibodies which immunospecifically bind to one or more RSV antigens reduces the dosage and frequency of administration of said antibodies to a subject.

The present invention is based, in part, upon achieving or inducing a serum titer of 1

20  $\mu\text{g}/\text{ml}$  or less, preferably 2  $\mu\text{g}/\text{ml}$  or less, 5  $\mu\text{g}/\text{ml}$  or less, 6  $\mu\text{g}/\text{ml}$  or less, 10  $\mu\text{g}/\text{ml}$  or less, 15  $\mu\text{g}/\text{ml}$  or less, 20  $\mu\text{g}/\text{ml}$  or less, or 25  $\mu\text{g}/\text{ml}$  or less of an antibody or fragment thereof that immunospecifically binds to a respiratory syncytial virus (RSV) antigen in a mammal with higher affinity and/or higher avidity than previously known antibodies, while reducing or avoiding adverse affects. Preferably a serum titer or serum titer of 1  $\mu\text{g}/\text{ml}$  or less, preferably 2  $\mu\text{g}/\text{ml}$  or less, 5  $\mu\text{g}/\text{ml}$  or less, 6  $\mu\text{g}/\text{ml}$  or less, 10  $\mu\text{g}/\text{ml}$  or less, 15  $\mu\text{g}/\text{ml}$  or less, 20  $\mu\text{g}/\text{ml}$  or less, or 25  $\mu\text{g}/\text{ml}$  or less is achieved approximately 20 days (preferably 25, 30, 35 or 40 days) after administration of a first dose of antibodies or fragments thereof which immunospecifically bind to a RSV antigen and without administration of any other doses of said antibodies or fragments thereof.

25 The present invention provides methods of achieving or inducing a serum titer of at least 30  $\mu\text{g}/\text{ml}$ , at least 40  $\mu\text{g}/\text{ml}$ , at least 50  $\mu\text{g}/\text{ml}$ , at least 75  $\mu\text{g}/\text{ml}$ , at least 100  $\mu\text{g}/\text{ml}$ , at least 125  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 175  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ , at least 225  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , at least 275  $\mu\text{g}/\text{ml}$ , at least 300  $\mu\text{g}/\text{ml}$ , at least 325  $\mu\text{g}/\text{ml}$ , at least 350  $\mu\text{g}/\text{ml}$ , at least 375  $\mu\text{g}/\text{ml}$ , or at least 400  $\mu\text{g}/\text{ml}$  of an antibody or fragment thereof that

30 immunospecifically binds to a respiratory syncytial virus (RSV) antigen in a mammal, while

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reducing or avoiding adverse affects. Preferably a serum titer or serum titer of at least 30  $\mu\text{g}/\text{ml}$ , preferably at least 40  $\mu\text{g}/\text{ml}$ , at least 50  $\mu\text{g}/\text{ml}$ , at least 75  $\mu\text{g}/\text{ml}$ , at least 100  $\mu\text{g}/\text{ml}$ , at least 125  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 175  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ , at least 225  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , at least 275  $\mu\text{g}/\text{ml}$ , at least 300  $\mu\text{g}/\text{ml}$ , at least 325  $\mu\text{g}/\text{ml}$ , at least 5 350  $\mu\text{g}/\text{ml}$ , at least 375  $\mu\text{g}/\text{ml}$ , or at least 400  $\mu\text{g}/\text{ml}$  is achieved approximately 30 days after administration of a first dose of antibodies or fragments thereof which immunospecifically bind to a RSV antigen and without administration of any other doses of said antibodies or fragments thereof.

In a specific embodiment, a serum titer in a non-primate mammal of at least 40 10  $\mu\text{g}/\text{ml}$ , preferably at least 80  $\mu\text{g}/\text{ml}$ , at least 100  $\mu\text{g}/\text{ml}$ , at least 120  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , or at least 300  $\mu\text{g}/\text{ml}$ , of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens is achieved at least 1 day after administering a dose of less than 2.5 mg/kg, preferably less than 1 mg/kg, or less than 0.5 mg/kg of the antibodies or antibody fragments to the non-15 primate mammal. In another embodiment, a serum titer in a non-primate mammal of at least 150  $\mu\text{g}/\text{ml}$ , preferably at least 200  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , at least 300  $\mu\text{g}/\text{ml}$ , at least 350  $\mu\text{g}/\text{ml}$ , or at least 400  $\mu\text{g}/\text{ml}$  of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens is achieved at least 1 day after administering a dose of approximately 5 mg/kg of the antibodies or antibody fragments to 20 the non-primate mammal.

In another embodiment, a serum titer in a primate of at least 40  $\mu\text{g}/\text{ml}$ , preferably at least 80  $\mu\text{g}/\text{ml}$ , at least 100  $\mu\text{g}/\text{ml}$ , at least 120  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , or at least 300  $\mu\text{g}/\text{ml}$  of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens is achieved at least 30 days after 25 administering a first dose of less than 5 mg/kg, preferably less than 3 mg/kg, less than 1 mg/kg, or less than 0.5 mg/kg of the antibodies or fragments thereof to the primate. In yet another embodiment, a serum titer in a primate of at least 200  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , at least 300  $\mu\text{g}/\text{ml}$ , at least 350  $\mu\text{g}/\text{ml}$ , or at least 400  $\mu\text{g}/\text{ml}$  of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens is achieved at 30 least 30 days after administering a first dose of approximately 15 mg/kg of the antibodies or fragments thereof to the primate. In accordance with these embodiments, the primate is preferably a human.

The present invention provides methods for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, 35 said methods comprising administering a first dose to said mammal of a prophylactically or

therapeutically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein said effective amount is less than 15 mg/kg of said antibodies or fragments thereof and which results in a serum titer of greater than 40  $\mu$ g/ml 30 days after the first administration and prior to any subsequent

5 administration. In one embodiment, RSV infection in a human subject is prevented or treated, or one or more symptoms associated with RSV infection is ameliorated by administering a first dose of less than 10 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, or less than 1 mg/kg of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens so that a serum antibody titer of at

10 least 40  $\mu$ g/ml, preferably at least 80  $\mu$ g/ml, or at least 120  $\mu$ g/ml, at least 150  $\mu$ g/ml, at least 200  $\mu$ g/ml, at least 250  $\mu$ g/ml, or at least 300  $\mu$ g/ml is achieved 30 days after the administration of the first dose of the antibodies or antibody fragments and prior to the administration of a subsequent dose. In another embodiment, RSV infection in a human subject is prevented or treated, or one or more symptoms associated with a RSV infection is

15 ameliorated by administering a first dose of approximately 15 mg/kg of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens so that a serum antibody titer of at least 75  $\mu$ g/ml, preferably at least 100  $\mu$ g/ml, at least 200  $\mu$ g/ml, at least 250  $\mu$ g/ml, at least 300  $\mu$ g/ml, at least 350  $\mu$ g/ml, or at least 400  $\mu$ g/ml is achieved 30 days after the administration of the first dose of the antibodies or antibody

20 fragments and prior to the administration of a subsequent dose. In yet another embodiment, RSV infection in a human subject is prevented or treated, or one or more symptoms associated with a RSV infection is ameliorated by administering a first dose of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens such that a prophylactically or therapeutically effective serum titer of less than 10  $\mu$ g/ml, preferably less than 5  $\mu$ g/ml, less than 3  $\mu$ g/ml, less than 1  $\mu$ g/ml, or less than 0.5  $\mu$ g/ml is achieved no more than 30 days after administering the antibodies or antibody fragments. In accordance with this embodiment, the first dose of one or more antibodies or fragments thereof is less than 10 mg/kg, preferably less than 5 mg/kg, less than 1 mg/kg, or less than 0.5 mg/kg.

25 30 The present invention provides antibodies or fragments thereof which immunospecifically bind to a RSV antigen with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . Preferably, the antibodies or antibody fragments have

a higher affinity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein. The present invention also provides pharmaceutical compositions comprising one or more antibodies which immunospecifically bind to a RSV antigen with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ .

The present invention also provides antibodies or fragments thereof which immunospecifically bind to a RSV antigen with a higher avidity than any previously known antibodies or fragments thereof. Preferably, the antibodies or antibody fragments have higher avidity for a RSV antigen than SYNAGIS® has for the RSV F glycoprotein. The present invention also provides antibodies or fragments thereof that immunospecifically bind to a RSV antigen which have a higher affinity for a RSV antigen than any previously known antibodies or fragments thereof. The present invention also provides pharmaceutical compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to a RSV antigen with a higher avidity than any previously known antibodies or fragments thereof.

The present invention also provides for antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  and which have a higher avidity for one or more RSV antigens than any previously known antibodies or fragments thereof such as, e.g., SYNAGIS®. The present invention further provides pharmaceutical compositions comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$  or at least  $5 \times 10^{15} \text{ M}^{-1}$  and which have a higher avidity for one or more RSV antigens than any previously known antibodies or fragments thereof such as, e.g., SYNAGIS®.

The present invention provides methods of achieving a certain serum titer (preferably a serum titer 1  $\mu\text{g/ml}$  or less, 2  $\mu\text{g/ml}$  or less, 5  $\mu\text{g/ml}$  or less, 6  $\mu\text{g/ml}$  or less, 10  $\mu\text{g/ml}$  or less, 15  $\mu\text{g/ml}$  or less, 20  $\mu\text{g/ml}$  or less, or 25  $\mu\text{g/ml}$  or less) of antibodies or

fragments thereof that immunospecifically bind to one or more RSV antigens in a mammal, said methods comprising administering to said mammal one or more antibodies or fragments thereof that have an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  for said RSV antigens. Preferably, the antibodies or antibody fragments have a higher affinity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein.

The present invention also provides methods of achieving a certain serum titer of antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens in a mammal, said methods comprising administering to said mammal one or more antibodies or fragments thereof that have a higher avidity for said RSV antigens than any previously known antibodies or antibody fragments. Preferably, the antibodies or antibody fragments have higher avidity for a RSV antigen than SYNAGIS® has for the RSV F glycoprotein.

The present invention also provides methods of achieving a certain serum titer of antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens in a mammal, said methods comprising administering to said mammal one or more antibodies or fragments thereof that have an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  for one or more RSV antigens and have a higher avidity than any previously known antibodies or antibody fragments for said RSV antigens.

The present invention also provides methods of neutralizing RSV using antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens and which have an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  for said RSV antigens. Preferably, the antibodies or antibody fragments have a higher affinity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein. The present invention also provides methods of neutralizing RSV using antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens and which have a higher avidity for said RSV antigens than any previously known antibodies or antibody fragments. Preferably,

the antibodies or antibody fragments have a higher avidity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein. The present invention also provides methods of neutralizing RSV using antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8$

5  $\text{M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  and which have a higher avidity for said RSV antigens than any previously known antibodies or antibody fragments. The higher affinity and/or higher

10 avidity that these antibodies or antibody fragments have for a RSV antigen results in a lower concentration of these antibodies or antibody fragments necessary to achieve neutralization of RSV than previously known.

The present invention also provides methods for preventing, treating or ameliorating one or more symptoms of RSV infection in a mammal, said methods comprising

15 administering to said mammal one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens and which have an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$  for said RSV antigens.

Preferably, the antibodies or antibody fragments have a higher affinity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein. The present invention also provides of methods preventing, treating or ameliorating one or more symptoms of RSV infection in a mammal, said methods comprising administering to said mammal one or more antibodies or

25 fragments thereof that immunospecifically bind to one or more RSV antigen and which have a higher avidity for said RSV antigen than any previously known antibodies or antibody fragments. Preferably, the antibodies or antibody fragments have a higher avidity for a RSV antigen than SYNAGIS® does for the RSV F glycoprotein. The present invention further provides methods of preventing, treating or ameliorating one or more

30 symptoms of RSV infection in a mammal, said methods comprising administering to said mammal one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at

least  $5 \times 10^{15} M^{-1}$  for said RSV antigen and which have a higher avidity for said RSV antigens than any previously known antibodies or antibody fragments. The higher affinity and/or higher avidity that these antibodies or antibody fragments have for a RSV antigen results in lower and/or less frequent doses of these antibodies or antibody fragments to

5 achieve a prophylactic or therapeutic effect in a mammal, preferably a human, than previously known.

The present invention provides methods for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a mammal, preferably a human, said methods comprising administering a first dose to said mammal of a prophylactically or

10 therapeutically effective amount of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with a higher avidity and/or affinity than previously known antibodies such as SYNAGIS®, wherein said effective amount is less than 15 mg/kg of said antibodies or fragments thereof and which results in a serum titer less than 30  $\mu$ g/ml (which is preferably at least 2  $\mu$ g/ml, more preferably at least 4  $\mu$ g/ml,

15 and most preferably at least 6  $\mu$ g/ml) 30 days after the first administration and prior to any subsequent administration. In one embodiment, RSV infection in a human subject is prevented or treated, or one or more symptoms in a human subject is ameliorated by administering a first dose of less than 10 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg, or less than 0.5 mg/kg of one or more antibodies or fragments

20 thereof that immunospecifically bind to one or more RSV antigens with a higher avidity and/or affinity than previously known antibodies such as SYNAGIS® so that a serum antibody titer of at least 6  $\mu$ g/ml, preferably at least 10  $\mu$ g/ml, at least 25  $\mu$ g/ml, at least 30  $\mu$ g/ml, at least 40  $\mu$ g/ml at least 80  $\mu$ g/ml, or at least 120  $\mu$ g/ml, at least 150  $\mu$ g/ml, at least 200  $\mu$ g/ml, at least 250  $\mu$ g/ml, or at least 300  $\mu$ g/ml is achieved 30 days after the

25 administration of the first dose of the antibodies or antibody fragments and prior to the administration of a subsequent dose.

The present invention provides antibodies or fragments thereof comprising a variable heavy ("VH") domain having an amino acid sequence of any VH domain listed in Table 2, and pharmaceutical compositions comprising said antibodies or antibody

30 fragments. The present invention also provides antibodies or fragments thereof comprising one or more VH CDRs having the amino acid sequence of one or more VH CDRs listed in Table 2 and/or Table 3, and pharmaceutical compositions comprising said antibodies or antibody fragments. The present invention also provides antibodies or fragments thereof comprising a variable light ("VL") domain having the amino acid sequence of any VL

35 domain listed in Table 2, and pharmaceutical compositions comprising said antibodies or

antibody fragments. The present invention also provides antibodies or fragments thereof comprising one or more VL CDRs having the amino acid sequence of one or more VL CDRs listed in Table 2 and/or Table 3, and pharmaceutical compositions comprising said antibodies or antibody fragments. The present invention also provides antibodies or

5 fragments thereof comprising a VH domain having the amino acid sequence any VH domain listed in Table 2 and a VL domain having the amino acid sequence of any VL domain listed in Table 2, and pharmaceutical compositions comprising said antibodies or antibody fragments. The present invention provides antibodies or fragments thereof comprising one or more VH CDRs having the amino acid sequence one or more VH CDRs

10 listed in Table 2 and/or Table 3 and one or more VL CDRs having the amino acid sequence of one or more VL CDRs listed in Table 2 and/or Table 3. The present invention encompasses pharmaceutical compositions comprising said antibodies or antibody fragments. Preferably, said antibodies or antibody fragments immunospecifically bind to one or more RSV antigens.

15 The present invention encompasses methods for preventing, treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising a variable heavy ("VH") domain having an amino acid sequence of any VH domain listed in Table 2. The present invention also encompasses methods for preventing, treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising one or more

20 VH CDRs having the amino acid sequence of one or more VH CDRs listed in Table 2 and/or Table 3. The present invention also encompasses methods for preventing, treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising a variable light ("VL") domain having the amino acid sequence of any VL domain listed in Table 2. The present invention also encompasses methods for preventing,

25 treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising one or more VL CDRs having the amino acid sequence of one or more VL CDRs listed in Table 2 and/or Table 3. The present invention also encompasses methods for preventing, treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising a VH domain having the amino acid sequence any VH domain

30 listed in Table 2 and a VL domain having the amino acid sequence of any VL domain listed in Table 2. The present invention further encompasses methods for preventing, treating, neutralizing and ameliorating one or more symptoms using one or more antibodies comprising one or more VH CDRs having the amino acid sequence one or more VH CDRs listed in Table 2 and/or Table 3 and one or more VL CDRs having the amino acid sequence

of one or more VL CDRs listed in Table 2 and/or Table 3. Preferably, said antibodies or antibody fragments immunospecifically bind to one or more RSV antigens.

The present invention encompasses antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with increased *in vivo* half-lives. In 5 particular, the present invention encompasses HL-SYNAGIS and antigen-binding fragments thereof. The present invention also encompasses novel antibodies or fragments thereof described herein which immunospecifically bind to one or more RSV antigens and have an Fc domain with a higher affinity for the FcRn receptor than the Fc domain of SYNAGIS®.

The present invention also encompasses methods for the prevention, neutralization, 10 treatment or amelioration of one or more symptoms associated with a RSV infection using antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with increased *in vivo* half-lives. In particular, the invention encompasses methods for the prevention, neutralization, treatment or amelioration of one or more symptoms associated with a RSV infection using HL-SYNAGIS or an antigen-binding fragment thereof. The 15 invention also encompasses methods for the prevention, neutralization, treatment or amelioration of one or more symptoms associated with a RSV infection using novel antibodies or fragments thereof described herein which immunospecifically bind to one or more RSV antigens and have an Fc domain with a higher affinity for the FcRn receptor than the Fc domain of SYNAGIS®.

20 The present invention provides sustained release formulations of antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens for the prevention, neutralization, treatment or amelioration of one or more symptoms associated with a RSV infection. In particular, the present invention provides sustained release formulations of SYNAGIS® or fragments thereof for the prevention, neutralization, 25 treatment or amelioration of one or more symptoms associated with a RSV infection. The present invention also provides sustained release formulations of one or more novel antibodies or fragments thereof described herein which immunospecifically bind to one or more RSV antigens for the prevention, neutralization, treatment or amelioration of one or more symptoms associated with a RSV infection.

30 The present invention also provides methods of administering compositions comprising antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens to the site of a RSV infection in a subject. In particular, the present invention provides compositions comprising one or more antibodies or fragments thereof for pulmonary delivery to a subject.

The present invention provides compositions comprising one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, and methods for detecting or diagnosing a RSV infection utilizing said antibodies or antibody fragments.

5            **5.1. Antibodies**

It should be recognized that antibodies that immunospecifically bind to a RSV antigen are known in the art. For example, SYNAGIS® is a humanized monoclonal antibody presently used for the prevention of RSV infection in pediatric patients. The present invention encompasses novel formulations for administration of SYNAGIS® and 10 other known anti-RSV antibodies and novel doses of SYNAGIS® and other known anti-RSV antibodies, as discussed herein.

In addition, the invention encompasses novel antibodies, fragments and other biological or macromolecules which immunospecifically bind to one or more RSV antigens. With respect to these novel agents, the invention further encompasses novel modes of 15 administration, doses, dosing and uses based, in part, upon their unique therapeutic profiles and potency.

Set forth below, is a more detailed description of the antibodies encompassed within the various aspects of the invention.

The present invention provides antibodies or fragments thereof that 20 immunospecifically bind to one or more RSV antigens. The present invention provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens. Preferably, the antibodies of the invention or fragments thereof immunospecifically bind to one or more RSV antigens regardless of the strain of RSV. The present invention also provides antibodies or fragments thereof that differentially or preferentially bind to RSV 25 antigens from one strain of RSV versus another RSV strain. In a specific embodiment, the antibodies of the invention or fragments thereof immunospecifically bind to the RSV F glycoprotein, G glycoprotein or SH protein. In a preferred embodiment, the antibodies present invention or fragments thereof immunospecifically bind to the RSV F glycoprotein. In another preferred embodiment, the antibodies of the present invention or fragments 30 thereof bind to the A, B, or C antigenic sites of the RSV F glycoprotein.

Antibodies of the invention include, but are not limited to, monoclonal antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, single-chain Fvs (scFv), single chain antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies 35 to antibodies of the invention), and epitope-binding fragments of any of the above. In

particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds to a RSV antigen. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, 5 IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule.

The antibodies of the invention may be from any animal origin including birds and mammals (*e.g.*, human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). Preferably, the antibodies of the invention are human or humanized monoclonal 10 antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice that express antibodies from human genes.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different 15 epitopes of a RSV polypeptide or may be specific for both a RSV polypeptide as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, *e.g.*, PCT publications WO 93/17715, WO 92/08802, WO 91/00360, and WO 92/05793; Tutt, et al., *J. Immunol.* 147:60-69(1991); U.S. Patent Nos. 4,474,893, 4,714,681, 4,925,648, 5,573,920, and 5,601,819; and Kostelny et al., *J. Immunol.* 148:1547-1553 20 (1992).

The present invention provides for antibodies or fragments thereof that exhibit a high potency in an assay described herein. High potency antibodies or fragments thereof can be produced by methods disclosed in copending U.S. patent application Serial Nos. 60/168,426 and 60/186,252 and methods described herein. For example, high potency 25 antibodies can be produced by genetically engineering appropriate antibody gene sequences and expressing the antibody sequences in a suitable host. The antibodies produced can be screened to identify antibodies with, *e.g.*, high  $k_{on}$  values in a BIACore assay.

The present invention provides for antibodies or fragments thereof that have a high binding affinity for one or more RSV antigens. In a specific embodiment, an antibody of 30 the present invention or fragment thereof has an association rate constant or  $k_{on}$  rate (antibody (Ab) + antigen (Ag)  $\xrightarrow{k_{on}}$  Ab-Ag) of at least  $10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1}\text{s}^{-1}$ . In a preferred embodiment, an antibody of the present invention or fragment thereof has a  $k_{on}$  of at least  $2 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1}\text{s}^{-1}$ .

In another embodiment, an antibody of the present invention or fragment thereof has a  $k_{off}$  rate (antibody (Ab) + antigen (Ag)  $\xleftarrow{K_{off}}$  Ab-Ag) of less than  $10^{-1} \text{ s}^{-1}$ , less than  $5 \times 10^{-1} \text{ s}^{-1}$ , less than  $10^{-2} \text{ s}^{-1}$ , less than  $5 \times 10^{-2} \text{ s}^{-1}$ , less than  $10^{-3} \text{ s}^{-1}$ , less than  $5 \times 10^{-3} \text{ s}^{-1}$ , less than  $10^{-4} \text{ s}^{-1}$ , less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5$   
5  $10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ , or less than  $10^{-10} \text{ s}^{-1}$ . In a preferred embodiment, an antibody of the present invention or fragment thereof has a  $k_{on}$  of less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5 \times 10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ ,  
10 or less than  $10^{-10} \text{ s}^{-1}$ .

In another embodiment, an antibody of the present invention or fragment thereof has an affinity constant or  $K_a$  ( $k_{on}/k_{off}$ ) of at least  $10^2 \text{ M}^{-1}$ , at least  $5 \times 10^2 \text{ M}^{-1}$ , at least  $10^3 \text{ M}^{-1}$ , at least  $5 \times 10^3 \text{ M}^{-1}$ , at least  $10^4 \text{ M}^{-1}$ , at least  $5 \times 10^4 \text{ M}^{-1}$ , at least  $10^5 \text{ M}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}$ , at least  $10^6 \text{ M}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}$ , at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . In yet another embodiment, an antibody or fragment thereof has a dissociation constant or  $K_d$  ( $k_{off}/k_{on}$ ) of less than  $10^{-2} \text{ M}$ , less than  $5 \times 10^{-2} \text{ M}$ , less than  $10^{-3} \text{ M}$ , less than  $5$   
15  $10^{-3} \text{ M}$ , less than  $10^{-4} \text{ M}$ , less than  $5 \times 10^{-4} \text{ M}$ , less than  $10^{-5} \text{ M}$ , less than  $5 \times 10^{-5} \text{ M}$ , less than  $10^{-6} \text{ M}$ , less than  $5 \times 10^{-6} \text{ M}$ , less than  $10^{-7} \text{ M}$ , less than  $5 \times 10^{-7} \text{ M}$ , less than  $10^{-8} \text{ M}$ , less than  $5 \times 10^{-8} \text{ M}$ , less than  $10^{-9} \text{ M}$ , less than  $5 \times 10^{-9} \text{ M}$ , less than  $10^{-10} \text{ M}$ , less than  $5 \times 10^{-10} \text{ M}$ , less than  $10^{-11} \text{ M}$ , less than  $5 \times 10^{-11} \text{ M}$ , less than  $10^{-12} \text{ M}$ , less than  $5 \times 10^{-12} \text{ M}$ , less than  $10^{-13} \text{ M}$ , less than  $5 \times 10^{-13} \text{ M}$ , less than  $10^{-14} \text{ M}$ , less than  $5 \times 10^{-14} \text{ M}$ , less than  $10^{-15} \text{ M}$ , or less than  $5 \times 10^{-15} \text{ M}$ .

The present invention provides antibodies or fragment thereof that have a median effective concentration ( $EC_{50}$ ) of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro*  
30 microneutralization assay. The median effective concentration is the concentration of antibody or antibody fragments that neutralizes 50% of the RSV in an *in vitro* microneutralization assay. In a preferred embodiment, antibody of the invention or fragment thereof has an  $EC_{50}$  of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM,  
35

less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay.

In a specific embodiment, an antibody of the present invention is SYNAGIS® or an antibody-binding fragment thereof (e.g., one or more complementarity determining regions (CDRs) of SYNAGIS®). The amino acid sequence of SYNAGIS® is disclosed, e.g., in Johnson et al., 1997, J. Infectious Disease 176:1215-1224, and U.S. Patent No. 5,824,307, each of which is incorporated herein by reference in its entirety. In alternative embodiment, an antibody of the present invention or fragment thereof is not SYNAGIS® or a fragment of SYNAGIS®, *i.e.*, is not an antibody comprising a VH domain of SEQ ID NO:7 and/or a VL 10 domain of SEQ ID NO:8.

The present invention provides for antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising the amino acid sequence of SYNAGIS® with one or more amino acid residue substitutions in the variable light (VL) domain and/or variable heavy (VH) domain 15 depicted in Figure 1. The present invention also provides for antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising the amino acid sequence of SYNAGIS® with one or more amino acid residue substitutions in one or more VL CDRs and/or one or more VH CDRs. In a specific embodiment, an antibody or fragment thereof comprises the amino acid 20 sequence of SYNAGIS® with one or more amino acid residue substitutions of the amino acid residues indicated in bold face and underlining in Table 1. In accordance with this embodiment, the amino acid residue substitutions can be conservative or non-conservative. The antibody or antibody fragment generated by introducing substitutions in the VH domain, VH CDRs, VL domain and/or VL CDRs of SYNAGIS® can be tested *in vitro* and 25 *in vivo*, for example, for its ability to bind to RSV F antigen, for its ability to neutralize RSV, or for its ability to prevent, treat or ameliorate one or more symptoms associated with a RSV infection.

Table 1. CDR Sequences Of SYNAGIS®

| CDR | Sequence                            | SEQ ID NO: |
|-----|-------------------------------------|------------|
| VH1 | <b>T<u>S</u>GMSVG</b>               | 1          |
| VH2 | <b>DIWW<u>DDKKD</u>YNPSLKS</b>      | 2          |
| VH3 | <b><u>S</u>MITN<u>WY</u>FDV</b>     | 3          |
| VL1 | <b>KC<u>QLS</u>VG<sup>Y</sup>MH</b> | 4          |
| VL2 | <b>D<u>TSK</u>LAS</b>               | 5          |
| VL3 | <b>F<u>QGSG</u>YP<u>F</u>T</b>      | 6          |

10      **Bold faced & underlined amino acid residues are preferred residues which should be substituted.**

In a specific embodiment, an antibody of the present invention is SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. Preferably, an antibody of the present invention is 15 AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. In another embodiment, an antibody is a Fab fragment 20 of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

25      AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, and A1h5 comprise the framework region and constant regions of SYNAGIS®. A4B4, A4B4(1), A4B4L1FR-S28R, and A4B4-F52S comprise the framework region and constant regions of SYNAGIS® with the exception that there is an amino acid substitution of an alanine for a valine at 30 position 109. In certain embodiments, A4B4, A4B4(1), A4B4L1FR-S28R, and A4B4-F52S comprise the framework region and constant regions of SYNAGIS®.

35      In another embodiment, the present invention provides for an antigen-binding fragment of AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. In another embodiment, the present invention provides for one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising a VH chain and/or VL chain having the amino acid sequence of a VH chain and/or VL chain of AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1),

A4B4L1FR-S28R, or A4B4-F52S. In another embodiment, the present invention provides for one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising a VH domain and/or VL domain having the amino acid sequence of a VH domain and/or VL domain of AFFF,

5 Pfl2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. In another embodiment, the present invention provides for antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising one or more CDRs having the

10 amino acid sequence of one or more CDRs of AFFF, Pfl2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. In yet another embodiment, the present invention provides for one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said

15 antibodies or antibody fragments comprising a combination of VH CDRs and/or VL CDRs having the amino acid sequence of VH CDRs and/or VL CDRs of AFFF, Pfl2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, and/or A4B4-F52S.

20 The present invention provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising a variable heavy ("VH") chain having an amino acid sequence of any one of the VL domains listed in Table 2. The present invention also provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said

25 antibodies or antibody fragments comprising a VH domain having an amino acid sequence of any one of the VH domains listed in Table 2. In certain embodiments of the invention, an antibody or fragment thereof comprising a VH domain having an amino acid of any of one of the VH domains listed in Table 2 is not SYNAGIS®. The present invention also provides antibodies or fragments thereof that immunospecifically bind to one or more RSV

30 antigens, said antibodies or fragments comprising a VH complementarity determining region ("CDR") having an amino acid sequence of any one of the VH CDRs listed in Table 2 and/or Table 3. In certain embodiments of the invention, an antibody or fragment thereof comprising a VH CDR having an amino acid of any of one of the VH CDRs listed in Table 2 and/or Table 3 is not SYNAGIS®.

Table 2. Antibodies &amp; Fragments Thereof

| Antibody Name | VH Chain       | VH Domain    | VH CDR1                | VH CDR2                          | VH CDR3                    | VL Chain      | VL Domain    | VL CDR1                    | VL CDR2                | VL CDR3                  |
|---------------|----------------|--------------|------------------------|----------------------------------|----------------------------|---------------|--------------|----------------------------|------------------------|--------------------------|
| **SYNAGIS     | SEQ ID NO: 208 | SEQ ID NO:7  | TSGMSVG (SEQ ID NO:1)  | DIWWDDKKDY NPSLKS (SEQ ID NO:2)  | SMITNWYFDV (SEQ ID NO:3)   | SEQ ID NO:209 | SEQ ID NO:8  | KCQLS VGYM H (SEQ ID NO:4) | DTSKLAS (SEQ ID NO:5)  | FQGSGYPFT (SEQ ID NO:6)  |
| ***AFFF       | SEQ ID NO: 210 | SEQ ID NO:9  | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDY NPSLKS (SEQ ID NO:2)  | SMITNEYFDV (SEQ ID NO:12)  | SEQ ID NO:211 | SEQ ID NO:13 | SASSVGYMH (SEQ ID NO:14)   | DTEKLAS (SEQ ID NO:15) | FQGSGYPFT (SEQ ID NO:16) |
| ***P122       | SEQ ID NO: 212 | SEQ ID NO:17 | TPGMSVG (SEQ ID NO:18) | DIWWDDKKHYN PSLKD (SEQ ID NO:19) | DMIFENFYFDV (SEQ ID NO:20) | SEQ ID NO:213 | SEQ ID NO:21 | SLS SRVGYMH (SEQ ID NO:22) | DTFLSS (SEQ ID NO:23)  | FQGSGYPFT (SEQ ID NO:6)  |
| ***P124       | SEQ ID NO: 214 | SEQ ID NO:24 | TPGMSVG (SEQ ID NO:18) | DIWWDGKKHYN PSLKD (SEQ ID NO:25) | DMIFENFYFDV (SEQ ID NO:20) | SEQ ID NO:215 | SEQ ID NO:26 | SLS SRVGYMH (SEQ ID NO:22) | DTRELPs (SEQ ID NO:27) | FQGSGYPFT (SEQ ID NO:6)  |
| ***P11d4      | SEQ ID NO: 216 | SEQ ID NO:28 | TPGMSVG (SEQ ID NO:18) | DIWWDGKKHYN PSLKD (SEQ ID NO:25) | DMIFENWYFDV (SEQ ID NO:29) | SEQ ID NO:217 | SEQ ID NO:30 | SPSSR VGYMH (SEQ ID NO:31) | DTMRLAS (SEQ ID NO:32) | FQGSGYPFT (SEQ ID NO:6)  |
| ***Ale9       | SEQ ID NO: 218 | SEQ ID NO:33 | TAGMSVG (SEQ ID NO:10) | DIWWDGKKHYN PSLKD (SEQ ID NO:25) | DMIFENWYFDV (SEQ ID NO:29) | SEQ ID NO:219 | SEQ ID NO:34 | SLS SRVGYMH (SEQ ID NO:22) | DTEKLSS (SEQ ID NO:35) | FQGSGYPFT (SEQ ID NO:6)  |
| ***A12a6      | SEQ ID NO: 220 | SEQ ID NO:36 | TAGMSVG (SEQ ID NO:10) | DIWWDGKKDY NPSLKD (SEQ ID NO:37) | DMIFENFYFDV (SEQ ID NO:20) | SEQ ID NO:221 | SEQ ID NO:38 | SASSRVGYMH (SEQ ID NO:39)  | DTEKLSS (SEQ ID NO:35) | FQGSGYPFT (SEQ ID NO:6)  |

|             |                |                             |         |                                  |                              |                              |                            |  |                         |
|-------------|----------------|-----------------------------|---------|----------------------------------|------------------------------|------------------------------|----------------------------|--|-------------------------|
| ***A13c4    | SEQ ID NO: 222 | SEQ ID NO:40 (SEQ ID NO:10) | TAGMSVG | DIWWDDGKSYN PSLKD (SEQ ID NO:41) | DMIFENFYFDV (SEQ ID NO:20)   | SEQ ID NO:42 (SEQ ID NO:22)  | SLSRVGYMH (SEQ ID NO:22)   | DTM <del>Y</del> QSS (SEQ ID NO:43)              | FQGSGYPFT (SEQ ID NO:6) |
| ***A17d4    | SEQ ID NO: 224 | SEQ ID NO:44 (SEQ ID NO:10) | TAGMSVG | DIWWDDGKSYN PSLKD (SEQ ID NO:45) | DMIFENFYFDV (SEQ ID NO:20)   | SEQ ID NO:46 (SEQ ID NO:25)  | LPSSRVGYM H (SEQ ID NO:47) | DTM <del>Y</del> QSS (SEQ ID NO:43)              | FQGSGYPFT (SEQ ID NO:6) |
| ***A4B4     | SEQ ID NO: 226 | SEQ ID NO:48 (SEQ ID NO:10) | TAGMSVG | DIWWDDKKH YNPSLK (SEQ ID NO:19)  | DMIFENFYFDV (SEQ ID NO:20)   | SEQ ID NO:49 (SEQ ID NO:27)  | SASSRVGYM H (SEQ ID NO:39) | D <del>T</del> EF <del>L</del> DS (SEQ ID NO:50) | FQGSGYPFT (SEQ ID NO:6) |
| ***A8c7     | SEQ ID NO: 228 | SEQ ID NO:51 (SEQ ID NO:10) | TAGMSVG | DIWWDDGKSYN PSLKD (SEQ ID NO:45) | DMIFENWYFDV V (SEQ ID NO:29) | SEQ ID NO:52 (SEQ ID NO:29)  | SPSSRVGYM H (SEQ ID NO:31) | D <del>T</del> RYQSS (SEQ ID NO:53)              | FQGSGYPFT (SEQ ID NO:6) |
| *IX-493L1FR | SEQ ID NO: 230 | SEQ ID NO:7 (SEQ ID NO:1)   | TSGMSVG | DIWWDDKKDYN PSLKS (SEQ ID NO:2)  | SMITNWYFDV (SEQ ID NO:3)     | SEQ ID NO:54 (SEQ ID NO:31)  | SASSSVGYMH (SEQ ID NO:14)  | DTSKLAS (SEQ ID NO:5)                            | FQGSGYPFT (SEQ ID NO:6) |
| *H3-3F4     | SEQ ID NO: 232 | SEQ ID NO:55 (SEQ ID NO:10) | TAGMSVG | DIWWDDKKDYN PSLKS (SEQ ID NO:2)  | DMIFENWYFDV (SEQ ID NO:29)   | SEQ ID NO:56 (SEQ ID NO:29)  | SASSSVGYMH (SEQ ID NO:14)  | D <del>T</del> YK <del>L</del> AS (SEQ ID NO:15) | FQGSGYPFT (SEQ ID NO:6) |
| *M3H9       | SEQ ID NO: 234 | SEQ ID NO:55 (SEQ ID NO:10) | TAGMSVG | DIWWDDKKDYN PSLKS (SEQ ID NO:2)  | DMIFENWYFDV (SEQ ID NO:29)   | SEQ ID NO:70 (SEQ ID NO:235) | SASSSVGYMH (SEQ ID NO:14)  | D <del>T</del> YK <del>T</del> S (SEQ ID NO:57)  | FQGSGYPFT (SEQ ID NO:6) |
| *Y10H6      | SEQ ID NO: 236 | SEQ ID NO:55 (SEQ ID NO:10) | TAGMSVG | DIWWDDKKDYN PSLKS (SEQ ID NO:2)  | DMIFENWYFDV (SEQ ID NO:29)   | SEQ ID NO:58 (SEQ ID NO:237) | SASSSVGYMH (SEQ ID NO:14)  | D <del>T</del> RY <del>L</del> S (SEQ ID NO:59)  | FQGSGYPFT (SEQ ID NO:6) |

|           |                |              |                        |                                   |                                   |               |              |                                 |                                 |                         |
|-----------|----------------|--------------|------------------------|-----------------------------------|-----------------------------------|---------------|--------------|---------------------------------|---------------------------------|-------------------------|
| *DG       | SEQ ID NO: 238 | SEQ ID NO:78 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDYN PSLKS (SEQ ID NO:2)   | <u>DMITNFYFDV</u> (SEQ ID NO:79)  | SEQ ID NO:239 | SEQ ID NO:56 | <u>SASSVGYM</u> (SEQ ID NO:14)  | DT <u>E</u> KLAS (SEQ ID NO:15) | FQGSGYPFT (SEQ ID NO:6) |
| AFFF(1)   | SEQ ID NO: 240 | SEQ ID NO:9  | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDYN PSLKS (SEQ ID NO:2)   | <u>SMITNFYFDV</u> (SEQ ID NO:12)  | SEQ ID NO:241 | SEQ ID NO:60 | <u>SASSVGYM</u> (SEQ ID NO:14)  | DT <u>E</u> KLAS (SEQ ID NO:15) | FQGSGYPFT (SEQ ID NO:6) |
| *6H8      | SEQ ID NO: 242 | SEQ ID NO:78 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDYN PSLKS (SEQ ID NO:2)   | <u>DMITNFYFDV</u> (SEQ ID NO:79)  | SEQ ID NO:243 | SEQ ID NO:62 | <u>SASSVGYM</u> (SEQ ID NO:14)  | DT <u>E</u> KLAS (SEQ ID NO:63) | FQGSGYPFT (SEQ ID NO:6) |
| *L1-7E5   | SEQ ID NO: 244 | SEQ ID NO:78 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDYN PSLKS (SEQ ID NO:2)   | <u>DMITNFYFDV</u> (SEQ ID NO:79)  | SEQ ID NO:245 | SEQ ID NO:64 | <u>SASSVGYM</u> (SEQ ID NO:39)  | DT <u>E</u> KLAS (SEQ ID NO:15) | FQGSGYPFT (SEQ ID NO:6) |
| *L2-15B10 | SEQ ID NO: 246 | SEQ ID NO:78 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKDYN PSLKS (SEQ ID NO:2)   | <u>DMITNFYFDV</u> (SEQ ID NO:79)  | SEQ ID NO:247 | SEQ ID NO:65 | <u>SASSVGYM</u> (SEQ ID NO:14)  | DT <u>E</u> KLAS (SEQ ID NO:66) | FQGSGYPFT (SEQ ID NO:6) |
| *A13a11   | SEQ ID NO: 248 | SEQ ID NO:67 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKHYN PSLKD (SEQ ID NO:19)  | <u>DMIFENWYFDV</u> (SEQ ID NO:29) | SEQ ID NO:249 | SEQ ID NO:68 | <u>SPSSRVGYM</u> (SEQ ID NO:31) | DT <u>YR</u> HSS (SEQ ID NO:69) | FQGSGYPFT (SEQ ID NO:6) |
| *A1h5     | SEQ ID NO: 250 | SEQ ID NO:33 | TAGMSVG (SEQ ID NO:10) | DIWWDGHKKHYN PSLKD (SEQ ID NO:25) | <u>DMIFENWYFDV</u> (SEQ ID NO:29) | SEQ ID NO:251 | SEQ ID NO:71 | <u>SLSSSVGYM</u> (SEQ ID NO:72) | DT <u>EF</u> RS (SEQ ID NO:73)  | FQGSGYPFT (SEQ ID NO:6) |
| A4B4(1)   | SEQ ID NO: 252 | SEQ ID NO:48 | TAGMSVG (SEQ ID NO:10) | DIWWDDKKHYN PSLKD (SEQ ID NO:19)  | <u>DMIFENWYFDV</u> (SEQ ID NO:20) | SEQ ID NO:253 | SEQ ID NO:74 | <u>SASSRVGYM</u> (SEQ ID NO:75) | DT <u>LL</u> DS (SEQ ID NO:75)  | FQGSGYPFT (SEQ ID NO:6) |

|                      |                      |                 |                                     |  |                                      |                      |                 |  |                              |                               |
|----------------------|----------------------|-----------------|-------------------------------------|--|--------------------------------------|----------------------|-----------------|--|------------------------------|-------------------------------|
| ***A4B4L1<br>FR-S28R | SEQ<br>ID NO:<br>254 | SEQ ID<br>NO:48 | <u>TAGMSVG</u><br>(SEQ ID<br>NO:10) | DIWWDDKK <u>H</u><br><u>YNPSLK<u>D</u></u><br>(SEQ ID NO:19) | <u>DMIFENFYFDV</u><br>(SEQ ID NO:20) | SEQ<br>ID NO:<br>255 | SEQ ID<br>NO:11 | <u>SASSR</u> <u>VGYM</u><br>H<br>(SEQ ID<br>NO:39) | DTSKLAS<br>(SEQ ID<br>NO:5)  | FQGSGYPFT<br>(SEQ ID<br>NO:6) |
| ***A4B4-<br>F2S      | SEQ<br>ID NO:<br>256 | SEQ ID<br>NO:48 | <u>TAGMSVG</u><br>(SEQ ID<br>NO:10) | DIWWDDKK <u>HYN</u><br><u>PSLK<u>D</u></u><br>(SEQ ID NO:19) | <u>DMIFENFYFDV</u><br>(SEQ ID NO:20) | SEQ<br>ID NO:<br>257 | SEQ ID<br>NO:76 | <u>SASSR</u> <u>VGYM</u><br>H<br>(SEQ ID NO:39)    | DTSFLDS<br>(SEQ ID<br>NO:77) | FQGSGYPFT<br>(SEQ ID<br>NO:6) |

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in SYNAGIS®; Fab fragment produced (\*); Monoclonal antibody produced (\*\*); Fab fragment & monoclonal antibody produced (\*\*\*)

Table 3. CDR Sequences

| VH CDR1                                     | VH CDR2   | VH CDR3  | VL CDR1  | VL CDR2  | VL CDR3  |
|---|---|--|--|--|--|
| T <u>G</u> GM <u>S</u> VG<br>(SEQ ID NO:1)  | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>D</u> <u>Y</u> NP <u>S</u> LK <u>S</u><br>(SEQ ID NO:2)   | <u>S</u> MT <u>I</u> <u>N</u> W <u>Y</u> FDV<br>(SEQ ID NO:3)  | <u>K</u> COL <u>S</u> VG <u>Y</u> MH<br>(SEQ ID NO:4)    | <u>D</u> TS <u>K</u> L <u>A</u> S<br>(SEQ ID NO:5)   | FQ <u>G</u> SG <u>Y</u> P <u>F</u> T<br>(SEQ ID NO:6)  |
| T <u>G</u> GM <u>S</u> VG<br>(SEQ ID NO:18) | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>H</u> YNP <u>S</u> LK <u>D</u><br>(SEQ ID NO:19)          | <u>D</u> MT <u>I</u> <u>N</u> F <u>Y</u> FDV<br>(SEQ ID NO:29) | <u>K</u> CO <u>S</u> SV <u>Y</u> MH<br>(SEQ ID NO:80)    | <u>D</u> TS <u>Y</u> L <u>A</u> S<br>(SEQ ID NO:81)  | FQ <u>E</u> SG <u>Y</u> P <u>F</u> T<br>(SEQ ID NO:6)  |
| T <u>A</u> GM <u>S</u> VG<br>(SEQ ID NO:10) | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>H</u> YNP <u>S</u> LK <u>S</u><br>(SEQ ID NO:82)          | <u>D</u> MT <u>I</u> <u>N</u> W <u>Y</u> FDV<br>(SEQ ID NO:83) | <u>K</u> CO <u>S</u> RV <u>Y</u> MH<br>(SEQ ID NO:84)    | <u>D</u> TS <u>Y</u> L <u>S</u> S<br>(SEQ ID NO:85)  | FQ <u>G</u> SG <u>Y</u> P <u>F</u> T<br>(SEQ ID NO:61) |
|   | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>D</u> <u>Y</u> NP <u>S</u> LK <u>D</u><br>(SEQ ID NO:86)  | <u>D</u> MI <u>E</u> N <u>F</u> YFDV<br>(SEQ ID NO:29)         | <u>K</u> COL <u>R</u> VG <u>Y</u> MH<br>(SEQ ID NO:87)   | <u>D</u> TK <u>K</u> L <u>S</u> S<br>(SEQ ID NO:88)  |  |
|   | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>H</u> YNP <u>S</u> LK <u>S</u><br>(SEQ ID NO:91)          | <u>D</u> MI <u>E</u> N <u>F</u> YFDV<br>(SEQ ID NO:20)         | <u>K</u> LO <u>L</u> SV <u>Y</u> MH<br>(SEQ ID NO:89)    | <u>D</u> TF <u>Y</u> L <u>S</u> S<br>(SEQ ID NO:90)  |  |
|   | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>D</u> <u>Y</u> NP <u>S</u> LK <u>D</u><br>(SEQ ID NO:93)  | <u>S</u> MT <u>I</u> <u>N</u> F <u>Y</u> FDV<br>(SEQ ID NO:12) | <u>K</u> LO <u>S</u> SV <u>Y</u> MH<br>(SEQ ID NO:92)    | <u>D</u> TE <u>K</u> L <u>S</u> S<br>(SEQ ID NO:15)  |  |
|   | DIWW <u>D</u> <u>G</u> <u>K</u> <u>K</u> <u>H</u> YNP <u>S</u> LK <u>D</u><br>(SEQ ID NO:25)          | <u>S</u> MT <u>I</u> <u>N</u> W <u>Y</u> FDV<br>(SEQ ID NO:94) | <u>K</u> LO <u>S</u> RV <u>Y</u> MH<br>(SEQ ID NO:95)    | <u>D</u> TF <u>K</u> L <u>S</u> S<br>(SEQ ID NO:96)  |  |
|   | DIWW <u>D</u> <u>G</u> <u>K</u> <u>K</u> <u>D</u> <u>Y</u> NP <u>S</u> LK <u>S</u><br>(SEQ ID NO:100) | <u>S</u> MI <u>E</u> N <u>F</u> YFDV<br>(SEQ ID NO:97)         | <u>K</u> LO <u>L</u> RV <u>Y</u> MH<br>(SEQ ID NO:98)    | <u>D</u> TF <u>Y</u> L <u>A</u> S<br>(SEQ ID NO:99)  |  |
|   | DIWW <u>D</u> <u>G</u> <u>K</u> <u>K</u> <u>D</u> <u>Y</u> NP <u>S</u> LK <u>D</u><br>(SEQ ID NO:103) |  | <u>K</u> LS <u>L</u> SV <u>Y</u> MH<br>(SEQ ID NO:101)   | <u>D</u> TS <u>K</u> L <u>P</u> S<br>(SEQ ID NO:102) |  |
|   | DIWW <u>D</u> <u>G</u> <u>K</u> <u>K</u> <u>H</u> YNP <u>S</u> LK <u>S</u><br>(SEQ ID NO:106)         |  | <u>K</u> LS <u>S</u> SV <u>Y</u> MH<br>(SEQ ID NO:104)   | <u>D</u> TS <u>G</u> L <u>A</u> S<br>(SEQ ID NO:105) |  |
|   | DIWW <u>D</u> <u>D</u> <u>K</u> <u>K</u> <u>S</u> YN <u>P</u> SL <u>K</u> <u>S</u><br>(SEQ ID NO:109) |  | <u>K</u> LS <u>S</u> RV <u>Y</u> MH<br>**(SEQ ID NO:107) | <u>D</u> TS <u>G</u> L <u>P</u> S<br>(SEQ ID NO:108) |  |

|  |   |                                    |
|--|---|------------------------------------|
| <u>DIWWDDKKSYNPSLKQ</u><br>(SEQ ID NO:111) | <u>KLSLRQVGYMH</u><br>(SEQ ID NO:110)   | <u>DTRGLPS</u><br>(SEQ ID NO:27)   |
| <u>DIWWDGKKSYNPSLKQ</u><br>(SEQ ID NO:114) | <u>KCSSLQVGYMH</u><br>(SEQ ID NO:112)   | <u>DTRKLAS</u><br>(SEQ ID NO:113)  |
| <u>DIWWDGKKSYNPSLKQ</u><br>(SEQ ID NO:41)  | <u>KCSSLQVGYMH</u><br>(SEQ ID NO:115)   | <u>DTRGLAS</u><br>(SEQ ID NO:116)  |
|  | <u>KCSSLQVGYMH</u><br>(SEQ ID NO:117)   | <u>DTRKLPs</u><br>(SEQ ID NO:118)  |
|  | <u>KCSSLRQVGYMH</u><br>(SEQ ID NO:119)  | <u>DTMRLAS</u><br>(SEQ ID NO:32)   |
|  | <u>SLSLSQVGYMH</u><br>(SEQ ID NO:120)   | <u>DTMQLAS</u><br>(SEQ ID NO:121)  |
|  | <u>SLSSSQVGYMH</u><br>(SEQ ID NO:122)   | <u>DTSRLAS</u><br>(SEQ ID NO:123)  |
|  | <u>SLSSSRQVGYMH</u><br>(SEQ ID NO:22)   | <u>DTSLLAS</u><br>(SEQ ID NO:124)  |
|  | <u>SLSLRLQVGYMH</u><br>(SEQ ID NO:125)  | <u>DTSLLLDs</u><br>(SEQ ID NO:126) |
|  | <u>SCQLSLSQVGYMH</u><br>(SEQ ID NO:127) | <u>DTSKLDS</u><br>(SEQ ID NO:128)  |
|  | <u>SCQSSSQVGYMH</u><br>(SEQ ID NO:129)  | <u>DTLLLDS</u><br>(SEQ ID NO:75)   |
|  | <u>SCQSSRLQVGYMH</u><br>(SEQ ID NO:130) | <u>DTLKLDs</u><br>(SEQ ID NO:131)  |

|  |  |
|--|--|
| <u>SCQLR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:132) | DT <u>LL</u> <sub>AS</sub><br>(SEQ ID NO:133)  |
| <u>SLQLS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:134) | DT <u>LK</u> <sub>AS</sub><br>(SEQ ID NO:135)  |
| <u>SLOSS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:136) | DT <u>SKL</u> <sub>SS</sub><br>(SEQ ID NO:137) |
| <u>SLQSR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:138) | DT <u>SKO</u> <sub>AS</sub><br>(SEQ ID NO:139) |
| <u>SLQLR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:140) | DT <u>SKO</u> <sub>SS</sub><br>(SEQ ID NO:141) |
| <u>SCSL</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:142)  | DT <u>SYL</u> <sub>AS</sub><br>(SEQ ID NO:143) |
| <u>SCSSS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:144) | DT <u>SYL</u> <sub>SS</sub><br>(SEQ ID NO:145) |
| <u>SCSSR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:146) | DT <u>SYQ</u> <sub>AS</sub><br>(SEQ ID NO:147) |
| <u>SCSLR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:148) | DT <u>SYQ</u> <sub>SS</sub><br>(SEQ ID NO:149) |
| <u>KPSSR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:150) | DT <u>MYQ</u> <sub>AS</sub><br>(SEQ ID NO:151) |
| <u>KPSLR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:152) | DT <u>MYQ</u> <sub>SS</sub><br>(SEQ ID NO:153) |
| <u>KPSSS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:153) | DT <u>MIK</u> <sub>AS</sub><br>(SEQ ID NO:154) |

|  |   |  |
|--|---|--|
|  | <u>KPSL</u> SVG <sub>Y</sub> MH<br>(SEQ ID NO:155)              | D <sub>T</sub> M <sub>K</sub> OSS<br>(SEQ ID NO:156) |
|  | <u>KPQSRV</u> GYMH<br>(SEQ ID NO:157)                           | D <sub>T</sub> MYLAS<br>(SEQ ID NO:158)              |
|  | <u>KPOLR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:159)              | D <sub>T</sub> MYLSS<br>(SEQ ID NO:160)              |
|  | <u>KPOSSV</u> GYMH<br>(SEQ ID NO:161)                           | D <sub>T</sub> M <sub>K</sub> LAS<br>(SEQ ID NO:162) |
|  | <u>KPOL</u> SVG <sub>Y</sub> MH<br>(SEQ ID NO:163)              | D <sub>T</sub> M <sub>K</sub> LSS<br>(SEQ ID NO:164) |
|  | <u>SPSSR</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:31)               | D <sub>T</sub> SKLSS<br>(SEQ ID NO:165)              |
|  | <u>SPS</u> L <sub>R</sub> VG <sub>Y</sub> MH<br>(SEQ ID NO:166) | D <sub>T</sub> RYQAS<br>(SEQ ID NO:167)              |
|  | <u>SPSS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:168)               | D <sub>T</sub> RYOSS<br>(SEQ ID NO:53)               |
|  | <u>SPSL</u> SVG <sub>Y</sub> MH<br>(SEQ ID NO:169)              | D <sub>T</sub> R <sub>K</sub> OAS<br>(SEQ ID NO:170) |
|  | <u>SPOS</u> RV <sub>Y</sub> GH<br>(SEQ ID NO:171)               | D <sub>T</sub> RK <sub>K</sub> SS<br>(SEQ ID NO:172) |
|  | <u>SPOL</u> RV <sub>Y</sub> MH<br>(SEQ ID NO:173)               | D <sub>T</sub> R <sub>K</sub> LAS<br>(SEQ ID NO:174) |
|  | <u>SPOSS</u> VG <sub>Y</sub> MH<br>(SEQ ID NO:175)              | D <sub>T</sub> R <sub>K</sub> LSS<br>(SEQ ID NO:176) |

|  |  |                                   |
|--|--|-----------------------------------|
|  | <u>SPOL\$VGYMH</u><br>(SEQ ID NO:177)  | <u>DTRYLAS</u><br>(SEQ ID NO:178) |
|  | <u>KAQSRVGYMH</u><br>(SEQ ID NO:179)   | <u>DTRYLSS</u><br>(SEQ ID NO:59)  |
|  | <u>KAOLR\$VGYMH</u><br>(SEQ ID NO:180) | <u>DTEFLDS</u><br>(SEQ ID NO:50)  |
|  | <u>KAQSSVGYMH</u><br>(SEQ ID NO:181)   | <u>DTSEFLDS</u><br>(SEQ ID NO:77) |
|  | <u>KAOL\$VGYMH</u><br>(SEQ ID NO:182)  |                                   |
|  | <u>KASSRVGYMH</u><br>(SEQ ID NO:183)   |                                   |
|  | <u>KASLRVGYMH</u><br>(SEQ ID NO:184)   |                                   |
|  | <u>KASSSVGYMH</u><br>(SEQ ID NO:185)   |                                   |
|  | <u>KASLSVGYMH</u><br>(SEQ ID NO:186)   |                                   |
|  | <u>SASSRVGYMH</u><br>(SEQ ID NO:39)    |                                   |
|  | <u>SASLRVGYMH</u><br>(SEQ ID NO:187)   |                                   |
|  | <u>SASSSVGYMH</u><br>(SEQ ID NO:14)    |                                   |

|  |   |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|
|  | <u>SASLSVGV</u> YMH<br>(SEQ ID NO:188)  |  |  |  |  |  |  |  |
|  | <u>SAOSR</u> VGVYMH<br>(SEQ ID NO:189)  |  |  |  |  |  |  |  |
|  | <u>SAQLR</u> VGVYMH<br>(SEQ ID NO:190)  |  |  |  |  |  |  |  |
|  | <u>SAQSS</u> VGVYMH<br>(SEQ ID NO:191)  |  |  |  |  |  |  |  |
|  | <u>LPS</u> SRVGVYMH<br>(SEQ ID NO:47)   |  |  |  |  |  |  |  |
|  | <u>LPSL</u> SVGVYMH<br>(SEQ ID NO:192)  |  |  |  |  |  |  |  |
|  | <u>LPS</u> SSVGVYMH<br>(SEQ ID NO:193)  |  |  |  |  |  |  |  |
|  | <u>LPSL</u> RVGVYMH<br>(SEQ ID NO:194)  |  |  |  |  |  |  |  |
|  | <u>LCSSR</u> VGVYMH<br>(SEQ ID NO:195)  |  |  |  |  |  |  |  |
|  | <u>LCSSL</u> RVGVYMH<br>(SEQ ID NO:196) |  |  |  |  |  |  |  |
|  | <u>LCSSS</u> VGVMH<br>(SEQ ID NO:197)   |  |  |  |  |  |  |  |
|  | <u>LC</u> SLRVGVYMH<br>(SEQ ID NO:198)  |  |  |  |  |  |  |  |

|  |                                      |  |  |  |  |  |  |  |  |
|--|--------------------------------------|--|--|--|--|--|--|--|--|
|  | <u>LPOSRVGYMH</u><br>(SEQ ID NO:199) |  |  |  |  |  |  |  |  |
|  | <u>LPQLSYGYMH</u><br>(SEQ ID NO:200) |  |  |  |  |  |  |  |  |
|  | <u>LPOSSVGYMH</u><br>(SEQ ID NO:201) |  |  |  |  |  |  |  |  |
|  | <u>LPQLRVGYMH</u><br>(SEQ ID NO:202) |  |  |  |  |  |  |  |  |
|  | <u>LCQSRVGYMH</u><br>(SEQ ID NO:203) |  |  |  |  |  |  |  |  |
|  | <u>LCQLSYGYMH</u><br>(SEQ ID NO:204) |  |  |  |  |  |  |  |  |
|  | <u>LCQSSVGYMH</u><br>(SEQ ID NO:205) |  |  |  |  |  |  |  |  |
|  | <u>LCQLRVGYMH</u><br>(SEQ ID NO:206) |  |  |  |  |  |  |  |  |
|  | <u>SAQLSYGYMH</u><br>(SEQ ID NO:207) |  |  |  |  |  |  |  |  |

In one embodiment of the present invention, antibodies or fragments thereof comprise a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18. In another embodiment, antibodies or fragments thereof comprise a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41 or SEQ ID NO:45. In another embodiment, antibodies comprise a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29 or SEQ ID NO:79. In a preferred embodiment, antibodies or fragments thereof comprise a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18, a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37 or SEQ ID NO:41, SEQ ID NO:45, and a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29 or SEQ ID NO:79.

The present invention also provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising a variable light ("VL") domain having an amino acid sequence of any one of the VL domains listed in Table 2. The present invention also provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or fragments comprising a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 2 and/or Table 3.

In one embodiment of the present invention, antibodies or fragments thereof comprise a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, or SEQ ID NO:47. In another embodiment, antibodies or fragments thereof comprise a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75 or SEQ ID NO:77. In another embodiment, antibodies or fragments thereof comprise a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61. In a preferred embodiment, antibodies or fragments thereof comprise a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, or SEQ ID NO:47, a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID

NO:75 or SEQ ID NO:77, and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61.

The present invention also provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or antibody

5 fragments comprising a VH domain disclosed herein combined with a VL domain disclosed herein, or other VL domain. The present invention further provides antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, said antibodies or fragments comprising a VL domain disclosed herein combined with a VH domain disclosed herein, or other VH domain. In a preferred embodiment, antibodies or fragments thereof

10 that immunospecifically bind to a RSV antigen comprise a VH domain having the amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67 or SEQ ID NO:78 and a VL domain having the amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID

15 NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76.

The present invention also provides antibodies or fragments thereof comprising one

20 or more VH CDRs and one or more VL CDRs listed in Table 2 and/or Table 3. In particular, the invention provides for an antibody or fragment thereof comprising a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any

25 combination thereof of the VH CDRs and VL CDRs listed in Table 2. The invention also provides for an antibody or fragment thereof comprising a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof of

30 the VH CDRs and VL CDRs listed in Table 3. The invention also provides for an antibody or fragment thereof comprising a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof of the VH CDRs and VL CDRs

35 listed in Table 2 and Table 3.

In one embodiment, an antibody or fragment thereof comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18 and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, or SEQ ID NO:47. In another embodiment, an antibody of

5 the present invention or fragment thereof comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18 and a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73,

10 SEQ ID NO:75, or SEQ ID NO:77. In another embodiment, an antibody of the present invention or fragment thereof comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18 and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61.

In another embodiment, an antibody of the present invention or fragment thereof

15 comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41 or SEQ ID NO:45 and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47. In another embodiment, an antibody of the present invention or fragment thereof comprises a VH CDR2 having the amino acid sequence of

20 SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41 or SEQ ID NO:45 and a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, or SEQ ID NO:77. In another

25 embodiment, an antibody of the present invention or fragment thereof comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41 or SEQ ID NO:45 and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

In another embodiment, an antibody of the present invention or fragment thereof

30 comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29 or SEQ ID NO:79 and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47. In another embodiment, an antibody of the present invention or fragment thereof comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

35 SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29 or SEQ ID NO:79 and a VL CDR2 having

the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, or SEQ ID NO:77. In a preferred embodiment, an antibody of the present

5 invention or fragment thereof comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29 or SEQ ID NO:79 and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

The present invention also provides for nucleic acid molecules, generally

10 isolated, encoding an antibody of the invention or fragment thereof. In a specific embodiment, isolated nucleic acid molecules of the invention encode for SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. Preferably, isolated nucleic acid molecules of the

15 invention encode for AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S. In another embodiment, isolated nucleic acid molecules of the invention encode for an antigen-binding fragment of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

In another embodiment, an isolated nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH domain having an amino acid sequence of any one of the VH domains listed in Table 2. In another embodiment, an isolated nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR1 having an amino acid sequence of any one of the VH CDR1s listed in Table 2 or Table 3. In another embodiment, an isolated nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR2 having an amino acid sequence of any one of the VH CDR2s listed in Table 2 or Table 3. In yet another embodiment, an isolated nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR3 having an amino acid sequence of any one of the VH CDR3s listed in Table 2 or Table 3.

In another embodiment, an isolated nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VL domain having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, an

isolated nucleic acid molecule(s) of the present invention encodes an antibody or fragment thereof comprising a VL CDR1 having amino acid sequence of any one of the VL CDR1s listed in Table 2 or Table 3. In another embodiment, an isolated nucleic acid molecule(s) of the present invention encodes an antibody or fragment thereof comprising a VL CDR2

5 having an amino acid sequence of any one of the VL CDR2s listed in Table 2 or Table 3. In yet another embodiment, an isolated nucleic acid molecule(s) of the present invention encodes an antibody or fragment thereof comprising a VL CDR3 having an amino acid sequence of any one of the VL CDR3s listed in Table 2 or Table 3.

In another embodiment, a nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH domain having an amino acid sequence of any one of the VH domains listed in Table 2 and a VL domain having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, a nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence listed in Table 2. In another embodiment, a nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence listed in Table 3. In another embodiment, a nucleic acid molecule(s) of the invention encodes an antibody or fragment thereof comprising a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence listed in Table 2 and Table 3.

The present invention also provides antibodies or fragments thereof comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that immunospecifically bind to an RSV antigen. The present invention also provides antibodies or fragments thereof comprising derivatives of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S, wherein said antibodies or fragments thereof immunospecifically bind to one or more RSV antigens. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions,

less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In a preferred embodiment, the derivatives have conservative amino acid substitutions made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which

5 the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine,

10 cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for

15 biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

In a specific embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises a nucleotide sequence that hybridizes to the nucleotide sequence(s) encoding SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45 °C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65 °C, under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 25 6xSSC at about 45 °C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68 °C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3).

30 In another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4,

A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

In a specific embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an amino acid sequence of a VH domain or an amino acid sequence a VL domain encoded by a nucleotide sequence that hybridizes to the nucleotide sequence encoding any one of the VH or VL domains listed in Table 2 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45 °C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65 °C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45 °C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68 °C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds. , 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an amino acid sequence of a VH CDR or an amino acid sequence of a VL CDRs encoded by a nucleotide sequence that hybridizes to the nucleotide sequence encoding any one of the VH CDRs or VL CDRs listed in Table 2 or Table 3 under stringent conditions *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45 °C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65 °C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45 °C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68 °C, or under other stringent hybridization conditions which are known to those of skill in the art. In yet another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an amino acid sequence of a VH CDR and an amino acid sequence of a VL CDR encoded by nucleotide sequences that hybridizes to the nucleotide sequences encoding any one of the VH CDRs and VL CDRs, respectively, listed in Table 2 or Table 3 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45 °C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65 °C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45 °C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68 °C, or under other stringent hybridization conditions which are known to those of skill in the art .

In another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an amino acid sequence of a VH domain that is at least

35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH domains listed in Table 2. In another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an 5 amino acid sequence of one or more VH CDRs that are at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any of the VH CDRs listed in Table 2 or Table 3.

In another embodiment, an antibody or fragment thereof that immunospecifically 10 binds to a RSV antigen comprises an amino acid sequence of a VL domain that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VL domains listed in Table 2. In another embodiment, an antibody or fragment thereof that immunospecifically binds to a RSV antigen comprises an 15 amino acid sequence of one or more VL CDRs that are at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any of the VL CDRs listed in Table 2 or Table 3.

In another embodiment, an antibody or fragment thereof that immunospecifically 20 binds to a RSV antigen comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, 25 L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S

The present invention also encompasses antibodies or fragments thereof that compete with an antibody or Fab fragment listed in Table 2 for binding to a RSV antigen. In particular, the present invention encompasses antibodies or fragments thereof that compete with SYNAGIS® or an antigen-binding fragment thereof for binding to the RSV F 30 glycoprotein. The present invention also encompasses VL domains, VH domains, VL CDRs, and VH CDRs that compete with a VL domain, VH domain, VL CDR, or VH CDR listed in Table 2 for binding to a RSV antigen. Further, the present invention encompasses VL CDRs and VL CDRs that compete with a VL CDR or VH CDR listed in Table 3 for binding to a RSV antigen.

The antibodies of the invention include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, 5 amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

10 The present invention also provides antibodies of the invention or fragments thereof that comprise a framework region known to those of skill in the art. Preferably, the framework region of an antibody of the invention or fragment thereof is human. In a specific embodiment, an antibody of the invention or fragment thereof comprises the framework region of SYNAGIS®.

15 The present invention also provides antibodies of the invention or fragments thereof that comprise constant regions known to those of skill in the art. Preferably, the constant regions of an antibody of the invention or fragment thereof are human. In a specific embodiment, an antibody of the invention or fragment thereof comprises the constant regions of SYNAGIS®.

20 The present invention also provides for antibodies or fragments thereof that have half-lives in a mammal, preferably a human, of greater than 15 days, preferably greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. The increased half-lives of the antibodies of the present

25 invention or fragments thereof in a mammal, preferably a human, results in a higher serum titer of said antibodies or antibody fragments in the mammal, and thus, reduces the frequency of the administration of said antibodies or antibody fragments and/or reduces the concentration of said antibodies or antibody fragments to be administered. Antibodies or fragments thereof having increased *in vivo* half-lives can be generated by techniques known

30 to those of skill in the art. For example, antibodies or fragments thereof with increased *in vivo* half-lives can be generated by modifying (*e.g.*, substituting, deleting or adding) amino acid residues identified as involved in the interaction between the Fc domain and the FcRn receptor (see, *e.g.*, PCT Publication No. WO 97/34631, which is incorporated herein by reference in its entirety). Such antibodies or fragments thereof can be tested for binding

activity to RSV antigens as well as for *in vivo* efficacy using methods known to those skilled in the art, for example, by immunoassays described herein.

Further, antibodies or fragments thereof with increased *in vivo* half-lives can be generated by attaching to said antibodies or antibody fragments polymer molecules such as 5 high molecular weight polyethyleneglycol (PEG). PEG can be attached to said antibodies or antibody fragments with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C- terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of 10 conjugation will be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, *e.g.*, size exclusion or ion-exchange chromatography. PEG-derivatized antibodies or fragments thereof can be tested for binding activity to RSV antigens as well as for *in vivo* efficacy using methods known to those skilled in the art, for 15 example, by immunoassays described herein.

The present invention also encompasses antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens, said antibodies or antibody fragments comprising the amino acid sequence of SYNAGIS® with mutations (*e.g.*, one or more amino acid substitutions) in the framework regions. In certain embodiments, 20 antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens comprise the amino acid sequence of SYNAGIS® with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains depicted in Figure 1. In a specific embodiment, antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens comprise the framework regions 25 depicted in Figure 2.

The present invention also encompasses antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens, said antibodies or fragments thereof comprising the amino acid sequence of SYNAGIS® with mutations (*e.g.*, one or more amino acid residue substitutions) in the variable and framework regions.

30 The present invention also provides for fusion proteins comprising an antibody or fragment thereof that immunospecifically binds to a RSV antigen and a heterologous polypeptide. Preferably, the heterologous polypeptide that the antibody or antibody fragment is fused to is useful for targeting the antibody to respiratory epithelial cells.

The present invention also provides for panels of antibodies or fragments thereof 35 that immunospecifically bind to an RSV antigen. In specific embodiments, the invention

provides for panels of antibodies or fragments thereof having different affinities for an RSV antigen, different specificities for an RSV antigen, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000 antibodies or fragments thereof. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

The present invention further provides for compositions comprising one or more antibodies of the invention or fragments thereof. In a specific embodiment, a composition of the present invention comprises SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, and/or A4B4-F52S. In another specific embodiment, a composition of the present invention comprises an antigen-binding fragment of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH domains having an amino acid sequence of any one of the VH domains listed in Table 2. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 or Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 or Table 3. In a preferred embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 or Table 3.

In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VL domains having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 or Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more

VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 or Table 3. In a preferred embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 or Table 3.

5 In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH domains having an amino acid sequence of any one of the VH domains listed in Table 2 and one or more VL domains having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, a composition of the present invention comprises one or more antibodies or  
10 fragments thereof comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 or Table 3 and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 or Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR1s having an amino acid  
15 sequence of any one of the VH CDR1s listed in Table 2 or Table 3 and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 or Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 or Table 3 and one or more VL  
20 CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 or Table 3.

In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 or Table 3 and one or more VL  
25 CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 or Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 or Table 3 and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 or  
30 Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 or Table 3 and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 or Table 3.

In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 or Table 3 and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 or

5 Table 3. In another embodiment, a composition of the present invention comprises one or more antibodies or fragments thereof comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 or Table 3 and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 or Table 3. In a preferred embodiment, a composition of the present invention comprises one

10 or more antibodies or fragments thereof comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 or Table 3 and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 or Table 3. In yet another embodiment, a composition of the present invention comprises one or more fusion proteins of the invention.

15 As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies or fragments thereof may further be recombinantly fused to a heterologous polypeptide at the N – or C- terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention

20 may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

Antibodies of the present invention or fragments thereof may be used, for example,

25 to purify, detect, and target RSV antigens, in both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies or fragments have use in immunoassays for qualitatively and quantitatively measuring levels of the RSV in biological samples such as sputum. See, e.g., Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

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### **5.1.1. Antibody Conjugates**

The present invention encompasses antibodies or fragments thereof recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least

35 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino

acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies may be used to target heterologous polypeptides to particular cell types (e.g., respiratory epithelial cells), either *in vitro* or *in vivo*, by fusing or conjugating the antibodies to antibodies specific for 5 particular cell surface receptors. Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See *e.g.*, PCT publication WO 93/21232; EP 439,095; Naramura *et al.*, Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies *et al.*, PNAS 89:1428-1432 (1992); and Fell *et al.*, J. Immunol. 146:2446-2452(1991), which are incorporated by 10 reference in their entirieties.

In one embodiment, a fusion protein of the invention comprises SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S and a heterologous polypeptide. In another embodiment, 15 a fusion protein of the invention comprises an antigen-binding fragment of SYNAGIS®, AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S and a heterologous polypeptide. In another embodiment, a fusion protein of the invention comprises one or more VH domains having the amino acid 20 sequence of any one of the VH domains listed in Table 2 or one or more VL domains having the amino acid sequence of any one of the VL domains listed in Table 2 and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises one or more VH CDRs having the amino acid sequence of any one of the VH CDRs listed in Table 2 or Table 3 and a heterologous polypeptide. In another embodiment, 25 a fusion protein comprises one or more VL CDRs having the amino acid sequence of any one of the VL CDRs listed in Table 2 or Table 3 and a heterologous polypeptide. In another embodiment, a fusion protein of the invention comprises at least one VH domain and at least one VL domain listed in Table 2 and a heterologous polypeptide. In yet another embodiment, a fusion protein of the invention comprises at least one VH CDR and at least 30 one VL CDR domain listed in Table 2 or Table 3 and a heterologous polypeptide.

The present invention further includes compositions comprising heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)<sub>2</sub> fragment, or portion thereof. Methods for fusing or conjugating polypeptides to 35 antibody portions are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603, 5,622,929,

5,359,046, 5,349,053, 5,447,851, and 5,112,946; EP 307,434; EP 367,166; PCT publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in 5 their entireties).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (e.g., antibodies or fragments thereof with 10 higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its 15 entirety). In one embodiment, antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody or antibody fragment, which portions immunospecifically bind to a RSV antigen may be recombined 20 with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies of the present invention or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a 25 pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from 30 the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a RSV infection as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. 35 Detection can be facilitated by coupling the antibody or fragment thereof to a detectable

substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or 5 fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of 10 suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of 15 suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

An antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, *e.g.*, a cytostatic or cytoidal agent, a therapeutic agent or a radioactive metal ion, *e.g.*, alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, 20 emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 25 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, 30 mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

Further, an antibody or fragment thereof may be conjugated to a therapeutic agent or drug moiety that modifies a given biological response. Therapeutic agents or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the 35 drug moiety may be a protein or polypeptide possessing a desired biological activity. Such

proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.*, TNF- $\alpha$ , TNF- $\beta$ , AIM I (see, International Publication No. WO 97/33899), AIM 5 II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, *J. Immunol.*, 6:1567-1574), and VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, *e.g.*, angiostatin or endostatin; or, a biological response modifier such as, for example, a lymphokine (*e.g.*, interleukin-1 ("IL- 1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating 10 factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (*e.g.*, growth hormone ("GH")).

Techniques for conjugating such therapeutic moieties to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 15 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of 20 Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, *Immunol. Rev.* 62:119-58.

An antibody or fragment thereof, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be 25 used as a therapeutic.

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

Antibodies may also be attached to solid supports, which are particularly useful for 30 immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

### 5.2. Prophylactic and Therapeutic Uses of Antibodies

The present invention is directed to antibody-based therapies which involve administering antibodies of the invention or fragments thereof to a mammal, preferably a human, for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection. Prophylactic and therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). Antibodies of the invention or fragments thereof may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

Antibodies of the present invention or fragments thereof that function as antagonists of a RSV infection can be administered to a mammal, preferably a human, to treat, prevent or ameliorate one or more symptoms associated with a RSV infection. For example, antibodies or fragments thereof which disrupt or prevent the interaction between a RSV antigen and its host cell receptor may be administered to a mammal, preferably a human, to treat, prevent or ameliorate one or more symptoms associated with a RSV infection.

In a specific embodiment, an antibody or fragment thereof prevents RSV from binding to its host cell receptor by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV binding to its host cell receptor in the absence of said antibodies or antibody fragments. In another embodiment, a combination of antibodies, a combination of antibody fragments, or a combination of antibodies and antibody fragments prevent RSV from binding to its host cell receptor by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV binding to its host cell receptor in the absence of said antibodies and/or antibody fragments.

Antibodies or fragments thereof which do not prevent RSV from binding its host cell receptor but inhibit or downregulate RSV replication can also be administered to a mammal to treat, prevent or ameliorate one or more symptoms associated with a RSV infection. The ability of an antibody or fragment thereof to inhibit or downregulate RSV replication may be determined by techniques described herein or otherwise known in the art. For example, the inhibition or downregulation of RSV replication can be determined by detecting the RSV titer in the lungs of a mammal, preferably a human.

In a specific embodiment, an antibody of the present invention or fragment thereof inhibits or downregulates RSV replication by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in absence of said antibodies or antibody fragments. In another embodiment, a combination of antibodies, a combination of antibody fragments, or a combination of antibodies and antibody fragments inhibit or downregulate RSV replication by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in absence of said antibodies and/or antibody fragments.

One or more antibodies of the present invention or fragments thereof that immunospecifically bind to one or more RSV antigens may be used locally or systemically in the body as a therapeutic. The antibodies of this invention or fragments thereof may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), which, for example, serve to increase the number or activity of effector cells which interact with the antibodies. The antibodies of this invention or fragments thereof may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), which, for example, serve to increase the immune response. The antibodies of this invention or fragments thereof may also be advantageously utilized in combination with one or more drugs used to treat RSV infection such as, for example anti-viral agents.

Antibodies of the invention or fragments may be used in combination with one or more of the following drugs: NIH-351 (Gemini Technologies), recombinant RSV vaccine (Aviron), RSVf-2 (Intracel), F-50042 (Pierre Fabre), T-786 (Trimeris), VP-36676 (ViroPharma), RFI-641 (American Home Products), VP-14637 (ViroPharma), PFP-1 and PFP-2 (American Home Products), RSV vaccine (Avant Immunotherapeutics), and F-50077 (Pierre Fabre).

The antibodies of the invention may be administered alone or in combination with other types of treatments (*e.g.*, hormonal therapy, immunotherapy, and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human or humanized antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent *in vivo* inhibiting antibodies and/or neutralizing antibodies that immunospecifically bind to a RSV antigen, for both immunoassays directed to RSV, prevention of RSV infection and therapy for RSV infection. It is also preferred to use polynucleotides encoding high affinity and/or potent *in vivo* inhibiting antibodies and/or neutralizing antibodies that immunospecifically bind to a RSV antigen, for both immunoassays directed to RSV and therapy for RSV infection. Such antibodies or fragments thereof will preferably have an affinity for the RSV F glycoprotein and/or fragments of the F glycoprotein.

In one embodiment, therapeutic or pharmaceutical compositions comprising antibodies of the invention or fragments thereof are administered to a mammal, preferably a human, to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In another embodiment, therapeutic or pharmaceutical compositions comprising antibodies of the invention or fragments thereof are administered to a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, or to a human who has had a bone marrow transplant to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In another embodiment, therapeutic or pharmaceutical compositions comprising antibodies of the invention or fragments thereof are administered to a human infant, preferably a human infant born prematurely or a human infant at risk of hospitalization for RSV infection to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In yet another embodiment, therapeutic or pharmaceutical compositions comprising antibodies of the invention or fragments thereof are administered to the elderly or people in group homes (e.g., nursing homes or rehabilitation centers).

In a specific embodiment, a mammal, preferably a human, is administered a therapeutic or pharmaceutical composition comprising one or more antibodies of the present invention or fragments thereof for the treatment, prevention or amelioration of one or more symptoms associated with a RSV infection in an amount effective for decreasing RSV titers. In accordance with this embodiment, an effective amount of antibodies or antibody fragments reduces the RSV titers in the lung as measured, for example, by the concentration of RSV in sputum samples or a lavage from the lungs from a mammal. In another embodiment, a mammal, preferably a human, is administered a therapeutic or pharmaceutical composition comprising one or more antibodies of the present invention or fragments thereof for the treatment, prevention or amelioration of symptoms associated with a RSV infection in an amount effective for inducing an immune response in the mammal.

In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition comprising less than 15 mg/kg, preferably less than 10 mg/kg, less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than previously known antibodies (e.g., SYNAGIS®) for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 1  $\mu$ g/ml, preferably at least 2  $\mu$ g/ml, at least 5  $\mu$ g/ml, at least 10  $\mu$ g/ml, at least 15  $\mu$ g/ml, at least 20  $\mu$ g/ml, or at least 25  $\mu$ g/ml 20 days (preferably 25, 30, 35, 40 days) after 5 the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said antibodies or antibody fragments is less than 30  $\mu$ g/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, said antibodies are AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, 10 L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, and A4B4-F52S.

In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition comprising less than 15 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which 15 immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than previously known antibodies (e.g., SYNAGIS®) for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 1  $\mu$ g/ml, preferably at least 2  $\mu$ g/ml, at least 5  $\mu$ g/ml, at least 10  $\mu$ g/ml, at least 15  $\mu$ g/ml, at least 20  $\mu$ g/ml, or at least 25  $\mu$ g/ml 25 days 20 after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said antibodies or antibody fragments is less than 30  $\mu$ g/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the novel antibodies are 25 AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3- 30 3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, and A4B4-F52S.

In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition comprising approximately 15 mg/kg of HL-SYNAGIS or antigen-binding fragments thereof for the prevention, treatment or 35 amelioration of one or more symptoms associated with a RSV infection in an amount

effective to induce a serum titer of at least 1  $\mu$ g/ml, preferably at least 30  $\mu$ g/ml, at least 35  $\mu$ g/ml, at least 40  $\mu$ g/ml, or at least 50  $\mu$ g/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. In another embodiment, a mammal, preferably a human, is administered a first dose of a

5 therapeutic or pharmaceutical composition comprising less than 15 mg/kg (preferably 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less) of HL-SYNAGIS or antigen-binding fragments thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 1  $\mu$ g/ml, preferably at least 30  $\mu$ g/ml, at least 35

10  $\mu$ g/ml, at least 40  $\mu$ g/ml, or at least 50  $\mu$ g/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

The present invention encompasses therapeutic or pharmaceutical compositions for pulmonary delivery comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher 15 avidity than previously known antibodies (e.g., SYNAGIS®). The present invention also encompasses therapeutic or pharmaceutical compositions for pulmonary delivery comprising SYNAGIS® or an antigen-binding fragment thereof.

In one embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition for pulmonary delivery comprising less than 15 20 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg, or less than 0.01 mg/kg of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than previously known antibodies (e.g., SYNAGIS®) for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount 25 effective to induce a titer of 20 ng per mg of lung protein (preferably at least 40 ng/mg, at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg) in an intubation sample or lavage from the lungs of said mammal 20 days (preferably 25, 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said 30 antibodies or antibody fragments is less than 100 ng/ml of protein 30 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the novel antibodies are AFFF, Pfl2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, and A4B4-F52S.

In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition for pulmonary delivery comprising approximately 15 mg/kg of SYNAGIS® or fragments thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount

5 effective to induce a titer of 20 ng per mg of lung protein (preferably at least 40 ng/mg, at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg) an intubation sample or lavage from the lungs of said mammal 30 days (preferably 35 or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. In another embodiment, a mammal,

10 preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition for pulmonary delivery comprising less than 15 mg/kg (preferably 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less) of SYNAGIS® or fragments thereof for the prevention of a RSV infection in an amount effective to induce a titer of 20 ng per mg of lung protein (preferably at least 40 ng/mg,

15 at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg) in an intubation sample or lavage from the lungs of said mammal 30 days (preferably 35 or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

The present invention encompasses therapeutic or pharmaceutical compositions for

20 pulmonary delivery comprising one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher avidity than previously known antibodies (e.g., SYNAGIS®). The present invention also encompasses therapeutic or pharmaceutical compositions for pulmonary delivery comprising HL-SYNAGIS or an antigen-binding

25 fragment thereof.

The present invention encompasses sustained release compositions comprising one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher avidity than previously known antibodies (e.g., SYNAGIS®). The present invention also

30 encompasses sustained release compositions comprising SYNAGIS® or an antigen-binding fragment thereof.

In one embodiment, a mammal, preferably a human, is administered a first dose of a sustained release formulation comprising less than 15 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of one or more antibodies or

35 fragments thereof which immunospecifically bind to one or more RSV antigens with higher

affinity and/or higher avidity than previously known antibodies (e.g., SYNAGIS®) for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 1  $\mu$ g/ml, preferably at least 2  $\mu$ g/ml, at least 5  $\mu$ g/ml, at least 10  $\mu$ g/ml, at least 15  $\mu$ g/ml, at least 20  $\mu$ g/ml, or at least 25  $\mu$ g/ml for at least 10 days (preferably at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said antibodies or antibody fragments is less than 30  $\mu$ g/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the novel antibodies are

10 AFFF, Pf12, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

In another embodiment, a mammal, preferably a human, is administered a first dose of a sustained release formulation comprising less than 15 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with higher affinity and/or higher avidity than previously known antibodies (e.g., SYNAGIS®) for the prevention, treatment, or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of 1  $\mu$ g/ml, preferably 2  $\mu$ g/ml, 5  $\mu$ g/ml, 10  $\mu$ g/ml, 15  $\mu$ g/ml, 20  $\mu$ g/ml, or 25  $\mu$ g/ml that is maintained for at least 10 days (preferably at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 days) after the administration of the first dose and prior to the administration of a subsequent dose without exceeding a serum titer of 30  $\mu$ g/ml.

In another embodiment, a mammal, preferably a human, is administered a first dose of a sustained release formulation comprising approximately 15 mg/kg of SYNAGIS® or fragments thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a titer of at least 30  $\mu$ g/ml, preferably at least 35  $\mu$ g/ml, at least 40  $\mu$ g/ml, or at least 50  $\mu$ g/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. In another embodiment, a mammal, preferably a human, is administered a first dose of a sustained release formulation comprising less than 15 mg/kg (preferably 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less) of SYNAGIS® or fragments thereof for the prevention of a RSV infection in an amount effective to induce at least 30  $\mu$ g/ml, preferably at least 35  $\mu$ g/ml, at least 40  $\mu$ g/ml, or at

least 50  $\mu\text{g}/\text{ml}$  25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a sustained release formulation comprising less than 15 mg/kg, preferably less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of 1  $\mu\text{g}/\text{ml}$ , preferably 2  $\mu\text{g}/\text{ml}$ , 5  $\mu\text{g}/\text{ml}$ , 10  $\mu\text{g}/\text{ml}$ , 15  $\mu\text{g}/\text{ml}$ , 20  $\mu\text{g}/\text{ml}$ , or 25  $\mu\text{g}/\text{ml}$  that is maintained for at least 10 days (preferably at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 days) after the administration of the first dose and prior to the administration of a subsequent dose without exceeding a serum titer of 30  $\mu\text{g}/\text{ml}$ .

The present invention encompasses sustained release formulations comprising one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher avidity than previously known antibodies such as, *e.g.*, SYNAGIS®. The present invention also encompasses sustained release formulations comprising HL-SYNAGIS or an antigen-binding fragment thereof.

The present invention encompasses sustained release formulations for pulmonary delivery comprising one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher avidity than previously known antibodies (*e.g.*, SYNAGIS®). The present invention also encompasses sustained release formulations for pulmonary delivery comprising one or more antibodies or fragments thereof which have increased *in vivo* half-lives and which immunospecifically bind to one or more RSV antigens with a higher affinity and/or a higher avidity than previously known antibodies (*e.g.*, SYNAGIS®). The present invention also encompasses sustained release formulations for pulmonary delivery comprising SYNAGIS® or fragments thereof. The present invention further encompasses sustained release formulations for pulmonary delivery comprising HL-SYNAGIS or an antigen-binding fragment thereof.

In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition comprising less than 10 mg/kg, less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg or less than 0.5 mg/kg of one or more antibodies of the present invention or fragments thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 35  $\mu\text{g}/\text{ml}$ , at least 40  $\mu\text{g}/\text{ml}$ , at least 50  $\mu\text{g}/\text{ml}$ , at least 80  $\mu\text{g}/\text{ml}$ , at least 100  $\mu\text{g}/\text{ml}$ , at least 120  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ ,

at least 250  $\mu\text{g}/\text{ml}$ , or at least 300  $\mu\text{g}/\text{ml}$  20 days (preferably 25, 30, 35 or 40 days) after the administration of the first dose. In another embodiment, a mammal, preferably a human, is administered a first dose of a therapeutic or pharmaceutical composition comprising approximately 15 mg/kg of one or more antibodies of the present invention or fragments thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a serum titer of at least 100  $\mu\text{g}/\text{ml}$ , at least 125  $\mu\text{g}/\text{ml}$ , at least 150  $\mu\text{g}/\text{ml}$ , at least 200  $\mu\text{g}/\text{ml}$ , at least 250  $\mu\text{g}/\text{ml}$ , at least 300  $\mu\text{g}/\text{ml}$ , at least 350  $\mu\text{g}/\text{ml}$ , at least 400  $\mu\text{g}/\text{ml}$ , or at least 450  $\mu\text{g}/\text{ml}$  20 days (preferably 25, 30, 35 or 40 days) after the administration of the first dose. The term "approximately 15 mg/kg" as used herein refers to a range of between 14 mg/kg and 16 mg/kg.

In another embodiment, a mammal, preferably a human, is administered a dose of a pharmaceutical composition comprising one or more antibodies of the present invention or fragments thereof for the prevention a RSV infection in an amount effective to induce a prophylactically effective serum titer of less than 10  $\mu\text{g}/\text{ml}$ , less than 8  $\mu\text{g}/\text{ml}$ , less than 5  $\mu\text{g}/\text{ml}$ , less than 3  $\mu\text{g}/\text{ml}$ , less than 1  $\mu\text{g}/\text{ml}$ , or less than 0.5  $\mu\text{g}/\text{ml}$  30 days after the administration of the dose, wherein said prophylactically effective serum titer is the serum titer that reduces the incidence of RSV infection in the human or the serum titer in a cotton rat that results in a RSV titer 5 days after challenge with  $10^5$  pfu RSV that is 99% lower than the RSV titer in the cotton rat 5 days after challenge with  $10^5$  pfu of RSV in a cotton rat not administered the dose prior to challenge. Preferably, the dose of the pharmaceutical composition comprises less than 10 mg/kg, less than 5 mg/kg, less than 3 mg/kg, less than 1 mg/kg, or less than 0.5 mg/kg of one or more antibodies of the present invention or fragments thereof.

In yet another embodiment, a mammal, preferably a human, is administered a dose of a therapeutic or pharmaceutical composition comprising one or more antibodies of the present invention or fragments thereof for the treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to induce a therapeutically effective serum titer of less than 10  $\mu\text{g}/\text{ml}$ , less than 8  $\mu\text{g}/\text{ml}$ , less than 5  $\mu\text{g}/\text{ml}$ , less than 3  $\mu\text{g}/\text{ml}$ , less than 1  $\mu\text{g}/\text{ml}$ , or less than 0.5  $\mu\text{g}/\text{ml}$  30 days after the administration of the dose, wherein said therapeutically effective serum titer is the serum titer that reduces the severity or length of RSV infection or is the serum titer in a cotton rat that results in a RSV titer in the rat 5 days after challenge with  $10^5$  pfu RSV that is 99% lower than the RSV titer 5 days after challenge with  $10^5$  pfu of RSV in a cotton rat not administered the dose prior to challenge. Preferably, the dose of the therapeutic or pharmaceutical composition comprises less than 12 mg/kg, less than 10 mg/kg, less than 5

mg/kg, less than 3 mg/kg, less than 1 mg/kg, or less than 0.5 mg/kg of one or more antibodies of the present invention or fragments thereof.

### 5.3. Methods of Administration of Antibodies

5 The invention provides methods of treatment, prophylaxis, and amelioration of one or more symptoms associated with RSV infection by administrating to a subject of an effective amount of antibody or fragment thereof, or pharmaceutical composition comprising an antibody of the invention or fragment thereof. In a preferred aspect, an antibody or fragment thereof is substantially purified (*i.e.*, substantially free from substances  
10 that limit its effect or produce undesired side-effects). The subject is preferably a mammal such as non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats etc.) and a primate (*e.g.*, monkey such as a cynomolgous monkey and a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely. In another embodiment, the subject is a human with cystic  
15 fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, a human who has had a bone marrow transplant, or an elderly human

Various delivery systems are known and can be used to administer an antibody of the invention or a fragment thereof, *e.g.*, encapsulation in liposomes, microparticles,  
20 microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering an antibody or fragment thereof, or pharmaceutical composition include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular,  
25 intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, antibodies of the present invention or fragments thereof, or pharmaceutical compositions are administered intramuscularly, intravenously, or subcutaneously. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous  
30 linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Patent Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and  
35 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO

98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety. In a preferred embodiment, an antibody of the invention or fragment thereof, or composition of the invention is administered using Alkermes AIR™ pulmonary drug delivery technology (Alkermes, Inc., Cambridge, MA).

5        The invention provides for any method of administrating lower doses of known antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens than previously thought to be effective for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. Preferably, lower doses of known antibodies or fragments thereof which immunospecifically bind to one or  
10 more RSV antigens are administered by pulmonary administration. The present invention also provides for any method of administering a novel antibody of the invention or fragment thereof for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. Preferably, novel antibodies of the invention or fragments thereof are administered by pulmonary administration.

15       The invention also provides that an antibody or fragment thereof is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of antibody or antibody fragment. In one embodiment, the antibody or antibody fragment is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, e.g., with water or saline to the appropriate  
20 concentration for administration to a subject. Preferably, the antibody or antibody fragment is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 5 mg, more preferably at least 10 mg, at least 15 mg, at least 25 mg, at least 35 mg, at least 45 mg, at least 50 mg, or at least 75 mg. The lyophilized antibody or antibody fragment should be stored at between 2 and 8°C in its original container and the  
25 antibody or antibody fragment should be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, an antibody or fragment thereof is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody or antibody fragment. Preferably, the liquid form of the antibody or fragment thereof is  
30 supplied in a hermetically sealed container at least 1 mg/ml, more preferably at least 2.5 mg/ml, at least 5 mg/ml, at least 8 mg/ml, at least 10 mg/ml, at least 15 mg/kg, or at least 25 mg/ml.

      In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved  
35 by, for example, and not by way of limitation, local infusion, by injection, or by means of an

implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a an antibody of the invention or fragment thereof, care must be taken to use materials to which the antibody or antibody fragment does not absorb.

5 In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat *et al.*, in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 3 17-327; see generally *ibid.*).

In yet another embodiment, the composition can be delivered in a controlled release  
10 or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:20; Buchwald *et al.*, 1980, *Surgery* 88:507; Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of the antibodies of the invention or fragments thereof (see *e.g.*, *Medical*  
15 *Applications of Controlled Release*, Langer and Wise (eds.), *CRC Pres.*, Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), *Wiley*, New York (1984); *Ranger and Peppas*, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 71:105); U.S. Patent No.  
20 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate),  
25 poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release  
30 system can be placed in proximity of the therapeutic target, *i.e.*, the lungs, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

Controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533). Any technique known to one of skill in the art can be used to produce  
35 sustained release formulations comprising one or more antibodies of the invention or

fragments thereof. See, e.g., U.S. Patent No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179-189, Song *et al.*, 1995, "Antibody Mediated Lung Targeting of

5 Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek *et al.*, 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam *et al.*, 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of

10 which is incorporated herein by reference in their entirety.

In a specific embodiment where the composition of the invention is a nucleic acid encoding an antibody or antibody fragment, the nucleic acid can be administered *in vivo* to promote expression of its encoded antibody or antibody fragment, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes

15 intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see *e.g.*, Joliot *et al.*, 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can

20 be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a prophylactically or therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment,

25 the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical

30 carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical

35 excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica

gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, 5 powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a prophylactically or therapeutically effective 10 amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to 15 human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

Generally, the ingredients of compositions of the invention are supplied either 20 separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile 25 water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived 30 from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the composition of the invention which will be effective in the treatment, prevention or amelioration of one or more symptoms associated with a RSV infection can be determined by standard clinical techniques. For example, the dosage of the 35 composition which will be effective in the treatment, prevention or amelioration of one or

more symptoms associated with a RSV infection can be determined by administering the composition to a cotton rat, measuring the RSV titer after challenging the cotton rat with  $10^5$  pfu of RSV and comparing the RSV titer to that obtain for a cotton rat not administered the composition. Accordingly, a dosage that results in a 2 log decrease or a 99% reduction

5 in RSV titer in the cotton rat challenged with  $10^5$  pfu of RSV relative to the cotton rat challenged with  $10^5$  pfu of RSV but not administered the composition is the dosage of the composition that can be administered to a human for the treatment, prevention or amelioration of symptoms associated with RSV infection. The dosage of the composition which will be effective in the treatment, prevention or amelioration of one or more

10 symptoms associated with a RSV infection can be determined by administering the composition to an animal model (e.g., a cotton rat or monkey) and measuring the serum titer of antibodies or fragments thereof that immunospecifically bind to a RSV antigen. Accordingly, a dosage of the composition that results in a serum titer of at least 1  $\mu$ g/ml, preferably 2  $\mu$ g/ml, 5  $\mu$ g/ml, 10  $\mu$ g/ml, 20  $\mu$ g/ml, 25  $\mu$ g/ml, at least 35  $\mu$ g/ml, at least 40

15  $\mu$ g/ml, at least 50  $\mu$ g/ml, at least 75  $\mu$ g/ml, at least 100  $\mu$ g/ml, at least 125  $\mu$ g/ml, at least 150  $\mu$ g/ml, at least 200  $\mu$ g/ml, at least 250  $\mu$ g/ml, at least 300  $\mu$ g/ml, at least 350  $\mu$ g/ml, at least 400  $\mu$ g/ml, or at least 450  $\mu$ g/ml can be administered to a human for the treatment, prevention or amelioration of one or more symptoms associated with RSV infection. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges.

20 The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the RSV infection, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model (e.g., the cotton rat or Cynomolgous monkey) test systems.

25 For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to

30 the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention or fragments thereof may be reduced by enhancing uptake and tissue penetration (e.g., into the lung) of the antibodies by modifications such as, for example, lipidation.

In a specific embodiment, antibodies of the invention or fragments thereof, or compositions comprising antibodies of the invention or fragments thereof are administered once a month just prior to or during the RSV season. In another embodiment, antibodies of the invention or fragments thereof, or compositions comprising antibodies of the invention or fragments thereof are administered every two months just prior to or during the RSV season. In yet another embodiment, antibodies of the invention or fragments thereof, or compositions comprising antibodies of the invention or fragments thereof are administered once just prior to or during the RSV season. The term "RSV season" refers to the season when RSV infection is most likely to occur. Typically, the RSV season in the northern hemisphere commences in November and lasts through April.

In one embodiment, approximately 5 mg/kg or less (preferably 1.5 mg/kg or less) of an antibody or fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or higher affinity than previously known antibodies such as, *e.g.*, SYNAGIS®, is administered five times, 3 times, or 1 to 2 times during a RSV season to a mammal, preferably a human. In another embodiment, approximately 1.5 mg/kg of an antibody or a fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or a higher affinity than known antibodies such as, *e.g.*, SYNAGIS®, is administered monthly five times during an RSV season to a mammal, preferably a human, intramuscularly. In another embodiment, 3 mg/kg of an antibody or a fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or a higher affinity than known antibodies such as, *e.g.*, SYNAGIS® is administered monthly three times during an RSV season to a mammal, preferably a human, intramuscularly. In yet another embodiment, 5 mg/kg of an antibody or a fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or a higher affinity than known antibodies such as, *e.g.*, SYNAGIS® is administered monthly one to two times during an RSV season to a mammal, preferably a human, intramuscularly.

In a specific embodiment, 15 mg/kg of HL-SYNAGIS or an antigen-binding fragment thereof is administered to a mammal, preferably a human, intramuscularly five times during an RSV season. In another embodiment, approximately 5 mg/kg or less (preferably 1.5 mg/kg or less) of an antibody or fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or higher affinity than previously known antibodies such as, *e.g.*, SYNAGIS®, is administered five times, 3 times, or 1 to 2 times during a RSV season to a mammal, preferably a human. In another embodiment, 3 mg/kg of antibody or a fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or a higher affinity known antibodies such as, *e.g.*, SYNAGIS® and

which has an increased *in vivo* half-life is administered monthly three times during an RSV season to a mammal, preferably a human, intramuscularly. In another embodiment, 5 mg/kg of antibody or a fragment thereof which immunospecifically binds to a RSV antigen with a higher avidity and/or a higher affinity than known antibodies such as, *e.g.*, SYNAGIS® and

5 which has an increased *in vivo* half-life is administered to a mammal, preferably a human, intramuscularly twice times during an RSV season.

In a specific embodiment, an approximately 15 mg/kg bolus of SYNAGIS® or an antigen-binding fragment thereof not in a sustained release formulation is administered to a mammal, preferably a human, and after a certain period of time less than 15 mg/kg

10 (preferably 5 mg/kg or less, more preferably 3 mg/kg or less, and most preferably 1.5 mg/kg or less) of SYNAGIS® or an antibody fragment in a sustained release is administered to said mammal intramuscularly two, three or four times during an RSV season. In accordance with this embodiment, a certain period of time can be 1 to 5 days, a week, two weeks, or a month. In another embodiment, approximately 15 mg/kg or less (preferably at least 2

15 mg/kg, at least 5 mg/kg, or at least 10 mg/kg) of SYNAGIS® or an antigen-binding fragment thereof in a sustained release formulation is administered to a mammal, preferably a human, intramuscularly two, three or four times during an RSV season.

In another embodiment, approximately 15 mg/kg or less (preferably at least 2 mg/kg, at least 5 mg/kg, or at least 10 mg/kg) of one or more antibodies or fragments thereof which

20 immunospecifically bind to one or more RSV antigens is administered to the lungs of a mammal by pulmonary delivery and then after a certain period of time (*e.g.*, 15 minutes, 30 minutes, 45 minutes, 1 hour, 6 hours, 12 hours, 1 day, 5 days, 10 days, 20 days, 25 days, 30 days, or 40 days) approximately 15 mg/kg or less of one or more said antibodies or antibody fragments is administered intramuscularly said mammal. In another embodiment,

25 approximately 15 mg/kg or less (preferably at least 2 mg/kg, at least 5 mg/kg, or at least 10 mg/kg) of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens is administered to a mammal intramuscularly and then after a certain period of time (*e.g.*, 15 minutes, 30 minutes, 45 minutes, 1 hour, 6 hours, 12 hours, 1 day, 5 days, 10 days, 20 days, 25 days, 30 days, or 40 days) approximately 15 mg/kg or less

30 of one or more said antibodies or antibody fragments is administered to the lungs of said mammal.

### **5.3.1. Gene Therapy**

In a specific embodiment, nucleic acids comprising sequences encoding antibodies

35 or functional derivatives thereof, are administered to treat, prevent or ameliorate one or

more symptoms associated with RSV infection, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded antibody or antibody fragment that mediates a prophylactic or therapeutic effect.

5 Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., 1993, Clinical Pharmacy 12:488-505; Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, Science 260:926-932 (1993); and 10 Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; May, 1993, TIBTECH 11(5):155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

15 In a preferred aspect, a composition of the invention comprises nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, 20 and, optionally, tissue- specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; Zijlstra et al., 1989, 25 Nature 342:435-438). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a subject may be either direct, in which case the subject is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in 30 which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the subject. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by 35 any of numerous methods known in the art, e.g., by constructing them as part of an

appropriate nucleic acid expression vector and administering it so that they become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or 5 cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid- 10 ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06180; WO 92/22635; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be 15 introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; and Zijlstra et al., 1989, *Nature* 342:435-438).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments thereof are used. For example, a retroviral vector 20 can be used (see Miller et al., 1993, *Meth. Enzymol.* 217:581-599). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a subject. More detail about retroviral vectors can be found in Boesen et al., 1994, 25 *Biotherapy* 6:291-302, which describes the use of a retroviral vector to deliver the mdr 1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., 1994, *J. Clin. Invest.* 93:644-651; Klein et al., 1994, *Blood* 83:1467-1473; Salmons and Gunzberg, 1993, *Human Gene Therapy* 4:129-141; and Grossman and Wilson, 30 1993, *Curr. Opin. in Genetics and Devel.* 3:110-114.

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, 35 and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing

cells. Kozarsky and Wilson, 1993, Current Opinion in Genetics and Development 3:499-503 present a review of adenovirus-based gene therapy. Bout et al., 1994, Human Gene Therapy 5:3-10 demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene 5 therapy can be found in Rosenfeld et al., 1991, Science 252:431-434; Rosenfeld et al., 1992, Cell 68:143-155; Mastrangeli et al., 1993, J. Clin. Invest. 91:225-234; PCT Publication W094/12649; and Wang et al., 1995, Gene Therapy 2:775-783. In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy 10 (Walsh et al., 1993, Proc. Soc. Exp. Biol. Med. 204:289-300; and U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a 15 selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a subject.

In this embodiment, the nucleic acid is introduced into a cell prior to administration 20 *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, 1993, Meth. Enzymol. 217:599-618; Cohen et al., 1993, Meth. Enzymol. 217:618-644; Clin. Pharma. Ther. 29:69-25 92 (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell 30 progeny.

The resulting recombinant cells can be delivered to a subject by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, 5 megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the subject.

10 In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in* 15 *vitro* can potentially be used in accordance with this embodiment of the present invention (see *e.g.*, PCT Publication WO 94/08598; Stemple and Anderson, 1992, Cell 71:973-985; Rheinwald, 1980, Meth. Cell Bio. 21A:229; and Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771).

15 In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

#### 5.4. Antibody Characterization and Demonstration of Therapeutic or Prophylactic Utility

25 Antibodies of the present invention or fragments thereof may be characterized in a variety of ways. In particular, antibodies of the invention or fragments thereof may be assayed for the ability to immunospecifically bind to a RSV antigen. Such an assay may be performed in solution (*e.g.*, Houghten, 1992, Bio/Techniques 13:412-421), on beads (Lam, 1991, Nature 354:82-84), on chips (Fodor, 1993, Nature 364:555-556), on bacteria (U.S. 30 Patent No. 5,223,409), on spores (U.S. Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (Cull et al., 1992, Proc. Natl. Acad. Sci. USA 89:1865-1869) or on phage (Scott and Smith, 1990, Science 249:386-390; Devlin, 1990, Science 249:404-406; Cwirla et al., 1990, Proc. Natl. Acad. Sci. USA 87:6378-6382; and Felici, 1991, J. Mol. Biol. 35 222:301-310) (each of these references is incorporated herein in its entirety by reference). 35 Antibodies or fragments thereof that have been identified to immunospecifically bind to a

RSV antigen or a fragment thereof can then be assayed for their specificity and affinity for a RSV antigen.

The antibodies of the invention or fragments thereof may be assayed for immunospecific binding to a RSV antigen and cross-reactivity with other antigens by any 5 method known in the art. Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, 10 agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not 15 intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium 20 vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to 25 immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

30 Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in 35 washing buffer (*e.g.*, PBS-Tween 20), blocking the membrane with primary antibody (the

antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in

5 blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

10 ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a

15 second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be

20 modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a

25 competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention or a fragment thereof for a RSV antigen and the binding off-rates can be determined from the data by scatchard plot analysis.

30 Competition with a second antibody can also be determined using radioimmunoassays. In this case, a RSV antigen is incubated with an antibody of the present invention or a fragment thereof conjugated to a labeled compound (*e.g.*,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding

35 on and off rates of antibodies or fragments thereof to a RSV antigen. BIAcore kinetic

analysis comprises analyzing the binding and dissociation of a RSV antigen from chips with immobilized antibodies or fragments thereof on their surface (see the Example section *infra*).

The antibodies of the invention or fragments thereof can also be assayed for their

5 ability to inhibit the binding of RSV to its host cell receptor using techniques known to those of skill in the art. For example, cells expressing the receptor for RSV can be contacted with RSV in the presence or absence of an antibody or fragment thereof and the ability of the antibody or fragment thereof to inhibit RSV's binding can be measured by, for example, flow cytometry or a scintillation assay. RSV (e.g., a RSV antigen such as F

10 glycoprotein or G glycoprotein) or the antibody or antibody fragment can be labeled with a detectable compound such as a radioactive label (e.g.,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^{125}\text{I}$ ) or a fluorescent label (e.g., fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin,  $\text{o}$ -phthaldehyde and fluorescamine) to enable detection of an interaction between RSV and its host cell receptor. Alternatively, the ability of antibodies or fragments

15 thereof to inhibit RSV from binding to its receptor can be determined in cell-free assays. For example, RSV or a RSV antigen such as G glycoprotein can be contacted with an antibody or fragment thereof and the ability of the antibody or antibody fragment to inhibit RSV or the RSV antigen from binding to its host cell receptor can be determined.

Preferably, the antibody or the antibody fragment is immobilized on a solid support and

20 RSV or a RSV antigen is labeled with a detectable compound. Alternatively, RSV or a RSV antigen is immobilized on a solid support and the antibody or fragment thereof is labeled with a detectable compound. RSV or a RSV antigen may be partially or completely purified (e.g., partially or completely free of other polypeptides) or part of a cell lysate. Further, an RSV antigen may be a fusion protein comprising the RSV antigen and a domain

25 such as glutathione-S-transferase. Alternatively, an RSV antigen can be biotinylated using techniques well known to those of skill in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL).

The antibodies of the invention or fragments thereof can also be assayed for their ability to inhibit or downregulate RSV replication using techniques known to those of skill

30 in the art. For example, RSV replication can be assayed by a plaque assay such as described, e.g., by Johnson et al., 1997, Journal of Infectious Diseases 176:1215-1224. The antibodies of the invention or fragments thereof can also be assayed for their ability to inhibit or downregulate the expression of RSV polypeptides. Techniques known to those of skill in the art, including, but not limited to, Western blot analysis, Northern blot analysis,

35 and RT-PCR can be used to measure the expression of RSV polypeptides. Further, the

antibodies of the invention or fragments thereof can be assayed for their ability to prevent the formation of syncytia.

The antibodies of the invention or fragments thereof are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans.

- 5 For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a subject tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a RSV infection (e.g., respiratory epithelial cells), to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans.
- 10 15 In a specific embodiment, cotton rats are administered an antibody the invention or fragment thereof, or a composition of the invention, challenged with  $10^5$  pfu of RSV, and four or more days later the rats are sacrificed and RSV titer and anti-RSV antibody serum titer is determined. Further, in accordance with this embodiment, the tissues (e.g., the lung tissues) from the sacrificed rats can be examined for histological changes.
- 20 25 In accordance with the invention, clinical trials with human subjects need not be performed in order to demonstrate the prophylactic and/or therapeutic efficacy of antibodies of the invention or fragments thereof. *In vitro* and animal model studies using the antibodies or fragments thereof can be extrapolated to humans and are sufficient for demonstrating the prophylactic and/or therapeutic utility of said antibodies or antibody fragments.
- 30 Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.
- 35 Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, to reduce the incidence of RSV infection, or to prevent, ameliorate or alleviate one or more symptoms associated with RSV infection. The treatment is considered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms, a reduction

in the duration of a RSV infection, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention. Further, the treatment is considered therapeutic if there is an increase in the immune response following the administration of one or more antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens.

Antibodies or compositions of the invention can be tested *in vitro* and *in vivo* for the ability to induce the expression of cytokines such as IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 and IL-15. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, an antibody or composition of the invention is tested for its ability to induce the expression of IFN- $\gamma$ .

Antibodies or compositions of the invention can be tested *in vitro* and *in vivo* for their ability to modulate the biological activity of immune cells, preferably human immune cells (e.g., T-cells, B-cells, and Natural Killer cells). The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells, detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by  $^3$ H-thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSA).

Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of RSV infection. Antibodies or compositions of the invention can also be

tested for their ability to increase the survival period of humans suffering from RSV infection by at least 25%, preferably at least 50%, at least 60%, at least 75%, at least 85%, at least 95%, or at least 99%. Further, antibodies or compositions of the invention can be tested for their ability reduce the hospitalization period of humans suffering from RSV infection by at least 60%, preferably at least 75%, at least 85%, at least 95%, or at least 99%. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

#### **5.5. Diagnostic Uses of Antibodies**

10 Labeled antibodies, fragments and derivatives and analogs thereof, which immunospecifically bind to a RSV antigen can be used for diagnostic purposes to detect, diagnose, or monitor a RSV infection. The invention provides for the detection of a RSV infection, comprising: (a) assaying the expression of a RSV antigen in cells or a tissue sample of a subject using one or more antibodies or fragments thereof that

15 immunospecifically bind to the RSV antigen; and (b) comparing the level of the RSV antigen with a control level, *e.g.*, levels in normal tissue samples not infected with RSV, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

The invention provides a diagnostic assay for diagnosing a RSV infection, comprising: (a) assaying for the level of a RSV antigen in cells or a tissue sample of an individual using one or more antibodies or fragments thereof that immunospecifically bind to a RSV antigen; and (b) comparing the level of the RSV antigen with a control level, *e.g.*, levels in normal tissue samples not infected with RSV, whereby an increase in the assayed RSV antigen level compared to the control level of the RSV antigen is indicative of a RSV infection. A more definitive diagnosis of RSV infection may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of RSV infection.

Antibodies of the invention or fragments thereof can be used to assay RSV antigen levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.*, see Jalkanen et al., 1985, *J. Cell. Biol.* 101:976-985; and Jalkanen et al., 1987, *J. Cell. Biol.* 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium

(<sup>3</sup>H); indium (<sup>111</sup>In), and technetium (<sup>99</sup>Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a RSV infection in a human. In one embodiment, diagnosis comprises: a) administering (for example, 5 parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody or fragment thereof that immunospecifically binds to a RSV antigen; b) waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject (e.g., the lungs) where the RSV antigen is expressed (and for unbound labeled molecule to be cleared to 10 background level); c) determining background level; and d) detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a RSV infection. Background level can be determined by various methods including, comparing the amount 15 of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99</sup>Tc. The labeled antibody or 20 antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

25 Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 30 5 to 10 days.

In one embodiment, monitoring of a RSV infection is carried out by repeating the method for diagnosing the RSV infection, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the subject using methods known 35 in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled

artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

5        In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal 10 and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### **5.6.        Methods Producing Antibodies**

15        The antibodies of the invention or fragments thereof can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

      Polyclonal antibodies to a RSV antigen can be produced by various procedures well known in the art. For example, a RSV antigen can be administered to various host animals 20 including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the RSV antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, 25 peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

      Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a 30 combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N. Y., 1981) (said references incorporated by reference in their entireties). The 35 term "monoclonal antibody" as used herein is not limited to antibodies produced through

hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with a RSV antigen and once an immune response is detected, *e.g.*, antibodies specific for the RSV antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with a RSV antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a RSV antigen.

Antibody fragments which recognize specific RSV epitopes may be generated by any technique known to those of skill in the art. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Further, the antibodies of the present invention can also be generated using various phage display methods known in the art.

In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of lymphoid tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector (e.g., p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen

binding domain that binds to a RSV antigen of interest can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., 1995, *J. Immunol. Methods* 182:41-50; Ames et al., 1995, *J. Immunol. Methods* 184:177-186; Kettleborough et al., 1994, *Eur. J. Immunol.* 24:952-958; Persic et al., 1997, *Gene* 187:9-18; Burton et al., 1994, *Advances in Immunology* 57:191-280; PCT application No. PCT/GB91/O1 134; PCT publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 10 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including 15 human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax et al., 1992, *BioTechniques* 12(6):864-869; Sawai 20 et al., 1995, *AJRI* 34:26-34; and Better et al., 1988, *Science* 240:1041-1043 (said references incorporated by reference in their entireties).

To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques 25 known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise an EF-1 $\alpha$  promoter, a secretion signal, a cloning site for the variable 30 domain, constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display 5 methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable 10 of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the 15 human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J<sub>H</sub> region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric 20 mice. The chimeric mice are then be bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes 25 harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human 30 antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, PCT publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be

engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, 1985, Science 229:1202; Oi et al., 1986, BioTechniques 4:214; Gillies et al., 1989, J. Immunol. Methods 125:191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, and 4,816,567, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering 7(6):805-814; and Roguska et al., 1994, PNAS 91:969-973), and chain shuffling (U.S. Patent No. 5,565,332). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the CDR3 listed in Table 2 and non-human framework regions. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; and Riechmann et al., 1988, Nature 332:323, which are incorporated herein by reference in their entireties.)

Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" RSV antigens using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, 1989, FASEB J. 7(5):437-444; and Nissinoff, 1991, J. Immunol. 147(8):2429-2438). For example, antibodies of the invention which bind to and competitively inhibit the binding of RSV (as determined by assays well known in the art and disclosed in *supra*) to its host cell receptor can be used to generate anti-idiotypes that "mimic" a RSV antigen binding domain and, as a consequence, bind to and neutralize RSV and/or its host cell receptor. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize RSV. For

example, such anti-idiotypic antibodies can be used to bind RSV and/or to bind its host cell receptors, and thereby block infection.

#### 5.6.1. Polynucleotides Encoding an Antibody

5 The invention provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention or a fragment thereof. The invention also encompasses polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides that encode an antibody of the invention.

10 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the antibodies are known (as described in Table 2), nucleotide sequences encoding these antibodies can be determined using methods well known in the art, *i.e.*, nucleotide codons known to encode particular amino acids are assembled in such a way to

15 generate a nucleic acid that encodes the antibody or fragment thereof of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier et al., 1994, BioTechniques 17:242), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then

20 amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a

25 suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to

30 identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the

35 manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed

mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel *et al.*, eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their 5 entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, one or more of the CDRs is inserted within framework regions using routine recombinant DNA techniques. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework 10 regions (see, *e.g.*, Chothia et al., 1998, *J. Mol. Biol.* 278: 457-479 for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds to a RSV antigen. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within 15 the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

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#### **5.6.2. Recombinant Expression of an Antibody**

Recombinant expression of an antibody of the invention, derivative or analog thereof, (*e.g.*, a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention), requires construction of an expression vector 25 containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods 30 for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic 35 recombination. The invention, thus, provides replicable vectors comprising a nucleotide

sequence encoding an antibody molecule of the invention, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a portion thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT 5 Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the 10 invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention or fragments thereof, or a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for 15 expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention (see, e.g., U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected 20 with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing 25 antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, 30 CHO, BHK, 293, NS0, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are 35 used for the expression of a recombinant antibody molecule. For example, mammalian

cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., 1986, Gene 45:101; and Cockett et al., 1990, Bio/Technology 8:2). In a specific embodiment, the expression of nucleotide sequences encoding antibodies or fragments thereof which immunospecifically bind to one or more RSV antigens is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

5 In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, 10 when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., 1983, EMBO 12:1791), in which the antibody coding sequence may be ligated individually 15 into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by 20 adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

25 In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

30 In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a 35 recombinant virus that is viable and capable of expressing the antibody molecule in infected

hosts (e.g., see Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 81:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired

5 coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., 1987, Methods in Enzymol. 153:51-544).

10 In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and

15 modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK,

20 HeLa, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7030 and Hs78Bst cells.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be

25 engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are

30 switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and

35 evaluation of compositions that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, Proc. Natl. Acad. Sci. USA 89:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:8-17) genes can

5 be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler et al., 1980, Natl. Acad. Sci. USA 77:357; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); *neo*, which confers

10 resistance to the aminoglycoside G-418 (Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62: 191-217; May, 1993, TIB TECH 11(5):155-2 15); and *hygro*, which confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147). Methods commonly known in the art of recombinant

15 DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-

20 Garapin et al., 1981, J. Mol. Biol. 150:1, which are incorporated by reference herein in their entirieties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, 25 Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., 1983, Mol. Cell. Biol. 3:257).

30 The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light

35 chain polypeptides. In such situations, the light chain should be placed before the heavy

chain to avoid an excess of toxic free heavy chain (Proudfoot, 1986, *Nature* 322:52; and Kohler, 1980, *Proc. Natl. Acad. Sci. USA* 77:2 197). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention or fragments thereof may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

#### 5.7. Kits

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that immunospecifically binds to a RSV antigen. In a specific embodiment, the kits of the present invention contain a substantially isolated RSV antigen as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with the RSV antigen. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a RSV antigen (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized RSV antigen. The RSV antigen provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which RSV antigen is attached. Such a kit may also include a non-attached

reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the RSV antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing RSV antigens. The diagnostic kit includes a substantially

5 isolated antibody specifically immunoreactive with a RSV antigen, and means for detecting the binding of the RSV antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled,

10 competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound RSV antigen obtained by the methods of the present invention. After the RSV antigen binds to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human

15 antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-RSV antigen antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

20 The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an

25 activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant RSV antigen, and a reporter-labeled anti-human antibody for detecting surface-bound anti-RSV antigen

30 antibody.

#### **6. EXAMPLE: KINETIC ANALYSIS OF HUMANIZED RSV MABS BY BIACORE™**

A typical kinetic study involved the injection of 250  $\mu$ l of monoclonal antibody

35 ("Mab") at varying concentrations (25-300 nM) in PBS buffer containing 0.05% Tween-20

(PBS/Tween). The flow rate was maintained at 75  $\mu$ l/min, giving a 15 minute dissociation time. Following the injection of Mab, the flow was exchanged with PBS/Tween buffer for 30 min for determining the rate of dissociation. The sensor chip was regenerated between cycles with a 1 min pulse of 100 mM HCl. The regeneration step caused a minimal loss of 5 binding capacity of the immobilized F-protein (4% loss per cycle). This small decrease did not change the calculated values of the rate constants for binding and dissociation (also called the  $k_{on}$  and  $k_{off}$ , respectively).

More specifically, for measurement of  $k_{assoc}$  (or  $k_{on}$ ), F protein was directly immobilized by the EDC/NHS method (EDC = N-ethyl-N'-[3-diethylaminopropyl]-10 carbodiimide). Briefly, 25 mg/ml of F protein in 10 mM NaOAc, pH 5.0 was prepared and about a 5-10  $\mu$ l injection gives about 30-50 RU (response units) of immobilized F protein under the above referenced conditions. The blank was subtracted for kinetic analysis. The column could be regenerated using 100 mM HCl (with 60 seconds of contact time being required for full regeneration). This treatment removed bound Fab completely without 15 damaging the immobilized antigen and could be used for over 40 regenerations. For  $k_{on}$  measurements, Fab concentrations were 0.39 nM, .75 nM, 1.56 nM, 3.13 nM, 12.5 nM, 25 nM, 50 nM, and 100 nM. The dissociation phase was analyzed for approximately 900 seconds. Kinetics were analyzed by 1:1 Langmuir fitting (global fitting). Measurements were done in HBS-EP buffer (10 mM HEPES, pH 7.4, 150 mM NaCl, 3 mM EDTA, 20 0.005% (v/v) Surfactant P20).

For measurements of combinatorial clones, as disclosed herein, the  $k_{on}$  and  $k_{off}$  were measured separately. The  $k_{on}$  was measured at conditions that were the same as those for the single mutation clones and was analyzed similarly.

For measuring  $k_{off}$ , the following conditions were employed. Briefly, 4100 RU of F 25 protein were immobilized (as above) with CM-dextran used as the blank. Here, 3000 RU of Fab was bound (with dissociated Fab high enough to offset machine fluctuation). HBS plus 5 nM F protein (about 350 – 2000 times higher than the  $K_d$  – the dissociation equilibrium constant) was used as buffer. The dissociation phase was 6 – 15 hours at a flow rate of 5 ml/min. Under the conditions used herein, re-binding of the dissociated Fab was minimal. 30 For further details, see the manual with the biosensor.

The binding of the high affinity anti-RSV antibodies to the F protein, or other epitopic sites on RSV, disclosed herein was calculated from the ratio of the first order rate constant for dissociation to the second order rate constant for binding or association ( $K_d = k_{off} / k_{on}$ ). The value for  $k_{on}$  was calculated based on the following rate equation:

$$dR/dt = k_{on}[Mab]R_{max} - (k_{on}[Mab] + k_{off})R$$

where  $R$  and  $R_{max}$  are the response units at time  $t$  and infinity, respectively. A plot of  $dr/dt$  as a function of  $R$  gives a slope of  $(k_a [Mab] + k_d)$ --since these slopes are linearly related to the  $[Mab]$ , the value  $k_{on}$  can be derived from a replot of the slopes versus  $[Mab]$ . The slope of the new line is equal to  $k_{on}$ . Although the value of  $k_{off}$  can be extrapolated from the Y-intercept, a more accurate value was determined by direct measurement of  $k_{off}$ . Following the injection phase of the Mab, PBS/Tween buffer flows across the sensor chip. From this point,  $[Mab]=0$ . The above stated equation for  $dR/dt$  thus reduces to:

10

$$dr/dt = k \quad \text{or} \quad dR/R = k_{off} dt$$

Integration of this equation then gives:

15

$$\ln(R_0/R_t) = k_{off} t$$

where  $R_0/R_t$  are the response units at time 0 (start of dissociation phase) and  $t$ , respectively. Lastly, plotting  $\ln(R_0/R_t)$  as a function of  $t$  gives a slope of  $k_{off}$ .

The numerical values from such antibody variants were as shown in Tables 4-7  
20 below.

Table 4. Summary of Kinetic Constants for High Potency Antibodies.

| ANTIBODY    | $K_{on} \times 10^5 (M^{-1}s^{-1})$ | $K_{off} \times 10^4 (s^{-1})$ | $EC_{50} (nM)$ |
|-------------|-------------------------------------|--------------------------------|----------------|
| **SYNAGIS®  | 2.04; 1.89; 2.18                    | 7.64; 7.38; 7.02               | 3.57           |
| **AFFF      | 1.08; 0.96; 1.24                    | 2.74; 2.66; 2.06               |                |
| *1X-493L1FR | 1.85                                | 6.5                            |                |
| *H3-3F4     | 4.59; 4.67; 5.72;<br>6.25; 5.33     | 4.45; 4.02                     |                |
| *M3H9       | 6.05                                | 3.38                           |                |
| *Y10H6      | 7.57                                | 4.62                           |                |
| *DG         | 2.65; 2.83; 4.16;<br>3.18; 2.88     | 1.67; 4.44                     |                |

|    |           |                                 |                  |      |
|----|-----------|---------------------------------|------------------|------|
|    | *AFFF     | 2.12; 1.56; 1.86                | 2.45; 4.46; 2.68 |      |
| 5  | *6H8      | 3.14; 4.44                      | 1.78; 4.73       |      |
|    | *L1-7E5   | 3.29; 3.57; 4.05;<br>3.35; 4.26 | 1.92; 3.31; 2.29 |      |
|    | *L2-15B10 | 3.69; 2.82; 3.12;<br>5.33; 3.78 | 1.34; 4.16; 2.70 |      |
| 10 | *P12f2    | 6.63                            | 2.82             | 0.65 |
|    | *P12f4    | 5.27                            | 2.99             | 0.70 |
| 15 | *P11d4    | 5.70; 5.72                      | 7.17             | >20  |
|    | *Ale9     | 7.9                             | 4.53             | 2.5  |
|    | *A12a6    | 7.43                            | 2.30             | 0.62 |
|    | *A13a11   | 7.35                            | 2.50             | 2.04 |
|    | *A13c4    | 7.81; 7.35                      | 2.80             | 0.52 |

Table 5.

Monoclonal Antibodies vs Bac-F (1:1)

|    |          | Kon (x E+5) | Koff (x E-5) | KD (nM)    | Chi2 |
|----|----------|-------------|--------------|------------|------|
| 20 | P12f2    | 4.07        | 12.8         | 0.31 (13)  | 0.9  |
|    | P12f4    | 4.95        | 5.55         | 0.11 (35)  | 0.6  |
|    | A13c4    | 3.00        | 3.96         | 0.13 (30)  | 1.2  |
| 25 | A12a6    | 4.60        | 1.65         | 0.04 (98)  | 1.2  |
|    | A1e9     | 4.33        | 14.3         | 0.33 (12)  | 2.5  |
|    | A8c7     | 4.17        | 8.75         | 0.21 (19)  | 1.8  |
|    | P11d4    | 4.66        | 28.9         | 0.62 (6)   | 1.0  |
|    | A17d4    | 4.56        | 4.07         | 0.09 (43)  | 0.5  |
| 30 | A4B4     | 4.34        | 1.06         | 0.02 (195) | 1.5  |
|    | SYNAGIS® | 1.32        | 51.5         | 3.90 (1)   | 0.6  |

Table 6.

| <u>Monoclonal Antibodies vs NUF4 (1:1)</u> |                    |                     |         |           |
|--|--------------------|---------------------|---------|-----------|
|  | <i>Kon</i> (x E+5) | <i>Koff</i> (x E-5) | KD (nM) | Chi2      |
|  | P12f2              | 5.41                | 17.8    | 0.33 (26) |
| 5  | P12f4              | 9.43                | 22.9    | 0.24 (36) |
|  | A13c4              | 3.65                | 27.2    | 0.75 (12) |
|  | A12a6              | 4.00                | 29.1    | 0.73 (12) |
|  | A1e9               | 8.43                | 58.4    | 0.69 (13) |
|  | A8c7               | 8.25                | 53.5    | 0.65 (13) |
| 10   | P11d4              | 9.04                | 76.6    | 0.85 (10) |
|  | A17d4              | 4.99                | 36.2    | 0.73 (12) |
|  | A4B4               | 4.96                | 28.2    | 0.57 (15) |
|  | SYNAGIS®           | 3.04                | 265     | 8.70 (1)  |
|  |                    |                     |         | 0.4       |

15 Table 7.

| <u>Monoclonal Antibodies vs NUF4 (2:1)</u> |                    |                     |         |            |
|--|--------------------|---------------------|---------|------------|
|  | <i>Kon</i> (x E+5) | <i>Koff</i> (x E-5) | KD (nM) | Chi2       |
|  | P12f2              | 2.82                | 23.6    | 0.84 (371) |
| 20   | P12f4              | 2.73                | 63.6    | 2.33 (134) |
|  | A13c4              | 3.20                | 22.5    | 0.70 (446) |
|  | A12a6              | 2.18                | 40.8    | 1.87 (167) |
|  | A1e9               | 3.29                | 139     | 4.22 (74)  |
|  | A8c7               | 4.30                | 114     | 2.65 (118) |
| 25   | P11d4              | 3.66                | 313     | 8.55 (36)  |
|  | A17d4              | 2.64                | 29.2    | 1.11 (281) |
|  | A4B4               | 2.03                | 40.06   | 2.00 (156) |
|  | SYNAGIS®           | 0.78                | 2420    | 312 (1)    |
|  |                    |                     |         | 1.3        |

1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF, 6H8, L1-7E5, L2-15B10, P12f2,  
 30 P12f4, P11d4, Ale9, A12a6, A13a11, and A13c4 are Fab fragments having the framework  
 sequences of Figure 1 and the indicated CDR sequences indicated listed in Table 2.  
 SYNAGIS AND AFFF are actual monoclonal antibodies with the framework sequences of  
 Figure 1 and constant regions as described in Johnson et al. (1997, Journal of Infectious  
 Diseases 176:1215-1224) and U.S. Patent No. 5,824,307. The framework sequences of  
 35 these antibodies may differ slightly from those of the Fab fragments.

The amino acid sequences of the indicated CDRs in Table 1 represent the amino acid residues located at the key locations within the CDRs of the high potency antibodies produced by the methods described herein and in copending applications Serial Nos. 60/168,426 and 60/186,252. For example, to increase the potency of an antibody by 5 producing a higher  $k_{on}$  value, the amino acids located at the key positions as taught herein by the bold and underlined residues in Table 1 for the reference antibody would be replaced by the amino acids listed under CDRs in Table 2 (and also bold and underlined). Thus, these one letter codes represent the amino acids replacing the reference amino acids at the key positions (or critical positions) of the CDRs shown in Figure 2 (residues in bold in the 10 sequences of Table 2) for a reference antibody whose potency is to be increased.

#### 7. EXAMPLE: MICRONEUTRALIZATION ASSAY

Neutralization of the antibodies of the present invention were determined by microneutralization assay. This microneutralization assay is a modification of the 15 procedures described by Anderson et al. (1985, J. Clin. Microbiol. 22:1050-1052, the disclosure of which is hereby incorporated by reference in its entirety). The procedure used here is described in Johnson et al., 1999, J. Infectious Diseases 180:35-40, the disclosure of which is hereby incorporated by reference in its entirety. Antibody dilutions were made in triplicate using a 96-well plate. Ten TCID<sub>50</sub> of respiratory syncytial virus (RSV - Long 20 strain) were incubated with serial dilutions of the antibody (or Fabs) to be tested for 2 hours at 37°C in the wells of a 96-well plate. RSV susceptible HEp-2 cells (2.5 x 10<sup>4</sup>) were then added to each well and cultured for 5 days at 37°C in 5% CO<sub>2</sub>. After 5 days, the medium was aspirated and cells were washed and fixed to the plates with 80% methanol and 20% PBS. RSV replication was then determined by F protein expression. Fixed cells were 25 incubated with a biotin-conjugated anti-F protein monoclonal antibody (pan F protein, C-site-specific MAbs 133-1H) washed and horseradish peroxidase conjugated avidin was added to the wells. The wells were washed again and turnover of substrate TMB (thionitrobenzoic acid) was measured at 450 nm. The neutralizing titer was expressed as the antibody concentration that caused at least 50% reduction in absorbency at 450 nm (the 30 OD<sub>450</sub>) from virus-only control cells. The results from the assay for the monoclonal antibodies and Fab fragments listed in Table 2 are shown in Table 4 *supra* and Table 8 *infra*.

Table 8. End Point RSV Microneutralization Titer Of High On Rate Mutant IgG and Fab

| Molecule   | Mean IC50 (Curve µg/ml) | STDEV Curve IC50 | Fold Difference (Curve ICX50) | Mean IC50 (Control) µg/ml | STDEV Control IC50 | Fold Difference (Control IC50) | n (assay repeat) |
|------------|-------------------------|------------------|-------------------------------|---------------------------|--------------------|--------------------------------|------------------|
| **SYNAGIS® | 0.4527                  | 0.208            | -                             | 0.5351                    | 0.238              | -                              | 8                |
| **A1e9     | 0.0625                  | 0.0268           | 7                             | 0.0645                    | 0.0223             | 8                              | 3                |
| **A17d4    | 0.0342                  | 0.022            | 13                            | 0.0354                    | 0.0187             | 15                             | 4                |
| **P11d4    | 0.0217                  | 0.0331           | 21                            | 0.0289                    | 0.0110             | 19                             | 5                |
| **P12f2    | 0.0231                  | 0.0141           | 20                            | 0.0223                    | 0.0083             | 24                             | 6                |
| **A8c7     | 0.0337                  | 0.0309           | 13                            | 0.0383                    | 0.0283             | 14                             | 5                |
| **A12a6    | 0.0357                  | 0.0316           | 13                            | 0.0354                    | 0.0261             | 15                             | 7                |
| **P12f4    | 0.0242                  | 0.0163           | 19                            | 0.0235                    | 0.0076             | 23                             | 7                |
| **A13c4    | 0.0376                  | 0.0268           | 12                            | 0.0375                    | 0.0213             | 14                             | 6                |
| **A4B4     | 0.0171                  | 0.0018           | 27                            | 0.0154                    | 0.00417            | 35                             | 2                |
| *A1e9      | 0.157                   | -                | 3                             | 0.125                     | -                  | 4                              | 1                |
| *A17d4     | 0.0179                  | -                | 25                            | 0.0171                    | -                  | 31                             | 1                |
| *P11d4     | >1.00                   | -                | -                             | >1.00                     | -                  | -                              | 1                |
| *P12f2     | 0.0407                  | 0.0112           | 11                            | 0.0326                    | 0.00905            | 16                             | 2                |
| *A8c7      | 0.177                   | -                | 3                             | 0.157                     | -                  | 34                             | 1                |
| *A12a6     | 0.0287                  | 0.00417          | 16                            | 0.0310                    | 0.00982            | 17                             | 2                |

|    |         |        |         |    |        |         |    |   |
|----|---------|--------|---------|----|--------|---------|----|---|
|    | *P12f4  | 0.0464 | 0.00791 | 10 | 0.0351 | 0.0126  | 15 | 2 |
|    | *A13c4  | 0.0264 | 0.00141 | 17 | 0.0258 | 0.00071 | 21 | 2 |
| 5  | *A4B4   | 0.0414 | -       | 11 | 0.0411 | -       | 13 | 1 |
|    | *A13a11 | 0.120  | 0.0222  | 4  | 0.1022 | 0.0260  | 5  | 2 |
| 10 | *A1h5   | 0.194  | 0.462   | 2  | 0.176  | 0.0625  | 3  | 2 |

\*\* Monoclonal Antibody

\* Fab Fragment

#### 8. EXAMPLE: RSV FUSION INHIBITION ASSAY

The ability of the antibodies of the invention or fragments thereof to block RSV-induced fusion after viral attachment to the cells is determined in a fusion inhibition assay. This assay is identical to the microneutralization assay, except that the cells were infected with RSV (Long) for four hours prior to addition of antibody (Taylor et al, 1992, J. Gen. Virol. 73:2217-2223).

#### 20 9. EXAMPLE: ISOTHERMAL TITRATION CALORIMETRY

Thermodynamic binding affinities and enthalpies were determined from isothermal titration calorimetry (ITC) measurements on the interaction of antibodies with RSV F glycoprotein (NUF4), an antigen which mimics the binding site of the RSV virus.

#### 25 Methods & Materials

##### Antibodies & Antigen

A13c4, A17d4, A4B4, and SYNAGIS® were diluted in dialysate and the concentrations were determined by UV spectroscopic absorption measurements with a Perkin-Elmer Lambda 4B Spectrophotometer using an extinction coefficient of 217,000 M<sup>-1</sup> cm<sup>-1</sup> at the peak maximum at 280 nm. The diluted NUF4 concentrations were calculated from the ratio of the mass of the original sample to that of the diluted sample since its extinction coefficient was too low to determine an accurate concentration without employing and losing a large amount of sample.

### ITC Measurements

The binding thermodynamics of the antibodies were determined from ITC measurements using a Microcal, Inc. VP Titration Calorimeter. The VP titration calorimeter consists of a matched pair of sample and reference vessels (1.409 ml) enclosed in an adiabatic enclosure and a rotating stirrer-syringe for titrating ligand solutions into the sample vessel. The ITC measurements were performed at 25 °C and 35 °C. The sample vessel contained the antibody in the phosphate buffer while the reference vessel contained just the buffer solution. The phosphate buffer solution was saline 67 mM PO<sub>4</sub> at pH 7.4 from HyClone, Inc. Five or ten  $\mu$ l aliquots of the 0.05 to 0.1 mM NUF4 solution were titrated 3 to 4 minutes apart into the antibody sample solution until the binding was saturated as evident by the lack of a heat exchange signal. With some antibody sample solutions, additional constant amounts of heat with the addition of each aliquot were observed following binding saturation of the antibody. This was attributed to a heat of dilution of the NUF4 titrant and was subtracted from the titrant heats obtained during the titration prior to analysis of the data.

A non-linear, least square minimization software program from Microcal, Inc., Origin 5.0, was used to fit the incremental heat of the *i*th titration ( $\Delta Q(i)$ ) of the total heat,  $Q_t$ , to the total titrant concentration,  $X_t$ , according to the following equations (1),

$$20 \quad Q_t = nC_t \Delta H_b V \{ 1 + X_t/nC_t + 1/nK_b C_t - [(1 + X_t/nC_t + 1/nK_b C_t)^2 - 4X_t/nC_t]^{1/2} \} / 2 \quad (1a)$$

$$\Delta Q(i) = Q(i) + dV_i/2V \{ Q(i) + Q(i-1) \} - Q(i-1) \quad (1b)$$

where  $C_t$  is the initial antibody concentration in the sample vessel,  $V$  is the volume of the sample vessel, and  $n$  is the stoichiometry of the binding reaction, to yield values of  $K_b$ ,  $\Delta H_b$ , and  $n$ . The optimum range of sample concentrations for the determination of  $K_b$  depends on the value of  $K_b$  and is defined by the following relationship.

$$C_t K_b n \leq 500 \quad (2)$$

30

so that at 1  $\mu$ M the maximum  $K_b$  that can be determined is less than  $2.5 \times 10^8 \text{ M}^{-1}$ . If the first titrant addition did not fit the binding isotherm, it was neglected in the final analysis since it may reflect release of an air bubble at the syringe opening-solution interface.

35

### Results

The ITC results are summarized in Table 9. The higher than 2 stoichiometries in Table 9 indicate that either the concentration determination of the antibody or NUF4 was incorrect. Since the same NUF4 sample was used as a titrant with antibodies having the 5 amino acid sequence of A13c4 at 35°C and A17d4 at 35°C, which exhibit in at least one of the titrations the correct stoichiometry of 2, it is assumed that the titrant concentration was correct and that the large values of n result from incorrectly determined antibody concentrations. However, it can be shown that the binding constants are critically dependent on the titrant concentration and, thus, despite the 2-3 disparity in n, the binding 10 constants are correct. Since the binding constants of antibodies having the amino acid sequence of A4B4 and A13c4 at 25°C were near the upper determination limit by ITC (equation 2) and with the limited amount of available NUF4, it was decided to use 35°C as the reference temperature for comprising the binding affinities. The results summarized in Table 9 show that the binding affinities to NUF4 are in the order A4B4 > A13c4 > A17d4 > 15 SYNAGIS®.

Table 9. Average Binding Constants and Enthalpies of NUF4 to Antibodies

| Antibody | $K_b$  | $\Delta H_b$ in $\text{kJ mol}^{-1}$ |
|----------|--|--------------------------------------|
| A4B4     | $269 \pm 74 \times 10^6 \text{ M}^{-1}$ or $\sim 3.7 \text{ nM}^*$ | $92.8 \pm 1.0$                       |
| A13c4    | $107 \pm 28 \times 10^6 \text{ M}^{-1}$ or $9 \text{ nM}$          | $67 \pm 17$                          |
| A17d4    | $75 \pm 14 \times 10^6 \text{ M}^{-1}$ or $13 \text{ nM}$          | $68 \pm 10$                          |
| SYNAGIS® | $1.23 \pm 0.17 \times 10^6 \text{ M}^{-1}$ or $810 \text{ nM}$     | $71 \pm 5$                           |

20 \* Based only on the best titration run at 35°C.

4.0 nM is ITC lower limit of  $1/K_b$  range (ITC range is limited to  $[\text{antibody}]_n K_b = 500$  where n is the stoichiometry and  $[\text{antibody}]$  is the concentration of the antibody in the cell).

#### **10. EXAMPLE: COTTON RAT PROPHYLAXIS**

30 To determine the ability of SYNAGIS® to prevent lower respiratory tract RSV infection in cotton rats when administered by and intravenous (IV) route and to correlate the serum concentration of SYNAGIS® with a reduction in lung RSV titer.

### Materials & Methods

SYNAGIS® lot L94H048 was used for studies III-47 and III-47A. SYNAGIS® lot L95 K016 was used for study III-58. Bovine serum albumin (BSA) (fraction V, Sigma Chemicals). RSV-Long (A subtype) was propagated in Hep-2 cells.

5 On day 0, to groups of cotton rats (*Sigmodon hispidus*, average weight 100 g) were administered SYNAGIS®, RSV-IGIV or BSA was administered by intramuscular injection. Twenty-four hours post administration, the animals were bled and infected intranasally with  $10^5$  pfu of RSV. Twenty-four hours later, the animals were bled and infected intranasally with  $10^5$  PFU or RSV (Long Strain). Four days after the infection, animals were sacrificed, 10 and their lung tissue was harvested and pulmonary virus titers were determined by plaque titration. For studies III-47 and III-47A, the doses of monoclonal antibody ("MAb") consisted of 0.31, 0.63, 1.25, 2.5, 5.5 and 10 mg/kg (body weight). For studies III-58, the doses of MAb consisted of 0.63, 1.25, 2.5, 5.5 and 10 mg/kg (body weight). In all three 15 studies bovine serum albumin (BSA) 10 mg/kg was used as a negative control. Human antibody concentrations in the serum at the time of challenge are determined using a sandwich ELISA.

### Results

The results of the individual experiments are presented in Tables 10-12. The results 20 of all of the experiments combined is shown in Table 13. All three studies show a significant reduction of pulmonary virus titers in animals treated with SYNAGIS®. A clear dose-response effect was observed in the animals. The combined data indicated that a dose of 2.5 mg/kg results in a greater than 99% reduction in lung RSV titer. The mean serum concentration of SYNAGIS® for this dose at the time of viral challenge was 28.6  $\mu$ g/ml.

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Table 10. EXPERIMENT III-47

| Compound    | Number of Animals | Dose       | Mean $\pm$ Std Error Concentration of Human IgG ( $\mu$ g/ml) | Lung Viral Titer Geometric Mean $\pm$ Std Error ( $\log_{10}$ pfu/gm) |
|-------------|-------------------|------------|---|---|
| 30 BSA      | 4                 |            | 0   | $1.4 \times 10^5 \pm 1.7$   |
| SYNAGIS®    | 3                 | 0.312mg/kg | 3.83 $\pm$ 1.1  | $2.1 \times 10^4 \pm 2.1$   |
| SYNAGIS®    | 3                 | 0.625mg/kg | 5.27 $\pm$ 0.37   | $7.7 \times 10^4 \pm 1.6$   |
| SYNAGIS®    | 4                 | 1.25mg/kg  | 9.15 $\pm$ 0.16   | $3.4 \times 10^4 \pm 1.3$   |
| SYNAGIS®    | 3                 | 2.50mg/kg  | 23.4 $\pm$ 2.8  | $1.4 \times 10^3 \pm 1.7$   |
| SYNAGIS®    | 2                 | 5.0mg/kg   | 42.4 $\pm$ 13.4   | $4.6 \times 10^2 \pm 4.6$   |
| 35 SYNAGIS® | 4                 | 10.0mg/kg  | 141.1 $\pm$ 14.4  | $1.0 \times 10^2 \pm 1.0$   |

Table 11. EXPERIMENT III-47A

| Compound | Number of Animals | Dose       | Mean±Std Error Concentration of Human IgG (µg/ml) | Lung Viral Titer Geometric Mean ±Std Error (log10 pfu/gm) |
|----------|-------------------|------------|---|---|
| 5 BSA    | 4                 |            | 0   | 1.9x10 <sup>5</sup> ±1.2                                  |
| SYNAGIS® | 4                 | 0.312mg/kg | 1.8±0.12  | 8.5x10 <sup>4</sup> ±1.2                                  |
| SYNAGIS® | 4                 | 0.625mg/kg | 4.0±0.19  | 5.0x10 <sup>4</sup> ±1.6                                  |
| SYNAGIS® | 4                 | 1.25mg/kg  | 11.8±0.68   | 1.9x10 <sup>3</sup> ±1.4                                  |
| SYNAGIS® | 4                 | 2.50mg/kg  | 18.9±2.0  | 5.3x10 <sup>3</sup> ±1.6                                  |
| SYNAGIS® | 3                 | 5.0mg/kg   | 55.6±2.3  | 1.6x10 <sup>2</sup> ±1.3                                  |
| SYNAGIS® | 4                 | 10.0mg/kg  | 109.7±5.22  | 1.0x10 <sup>2</sup> ±1.0                                  |

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Table 12. EXPERIMENT III-58

| Compound | Number of Animals | Dose       | Mean±Std Error Concentration of Human IgG (µg/ml) | Lung Viral Titer Geometric Mean ±Std Error (log10 pfu/gm) |
|----------|-------------------|------------|---|---|
| 15 BSA   | 4                 |            | 0   | 1.1x10 <sup>5</sup> ±1.2                                  |
| SYNAGIS® | 4                 | 0.625mg/kg | 5.78±0.32   | 1.6x10 <sup>4</sup> ±1.2                                  |
| SYNAGIS® | 4                 | 1.25mg/kg  | 9.82±0.23   | 1.6x10 <sup>3</sup> ±1.3                                  |
| SYNAGIS® | 4                 | 2.50mg/kg  | 34.1±2.11   | 4.3x10 <sup>2</sup> ±1.6                                  |
| SYNAGIS® | 3                 | 5.0mg/kg   | 58.3±4.48   | 1.0x10 <sup>2</sup> ±1.0                                  |
| SYNAGIS® | 4                 | 10.0mg/kg  | 111.5±5.04  | 1.0x10 <sup>2</sup> ±1.0                                  |

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Table 13. III-47, III-47A and III-58 COMBINED

| Compound    | Number of Animals | Dose       | Mean±Std Error Concentration of Human IgG (µg/ml) | Lung Viral Titer Geometric Mean ±Std Error (log10 pfu/gm) |
|-------------|-------------------|------------|---|---|
| BSA         | 18                |            | 0   | 1.3x10 <sup>5</sup> ±1.2                                  |
| 25 SYNAGIS® | 7                 | 0.312mg/kg | 2.67±0.60   | 4.6x10 <sup>4</sup> ±1.5                                  |
| SYNAGIS®    | 17                | 0.625mg/kg | 5.27±0.27   | 2.7x10 <sup>4</sup> ±1.3                                  |
| SYNAGIS®    | 18                | 1.25mg/kg  | 10.1±0.29   | 3.3x10 <sup>3</sup> ±1.4                                  |
| SYNAGIS®    | 17                | 2.50mg/kg  | 28.6±2.15   | 9.6x10 <sup>2</sup> ±1.5                                  |
| SYNAGIS®    | 15                | 5.0mg/kg   | 55.6±3.43   | 1.3x10 <sup>2</sup> ±1.2                                  |
| SYNAGIS®    | 18                | 10.0mg/kg  | 117.6±5.09  | 1.0x10 <sup>2</sup> ±1.0                                  |

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### 11. EXAMPLE: INTRAMUSCULAR COTTON RAT STUDIES

This experiment demonstrates that a greater reduction in RSV titer is achieved when A4b4, A4b4-F52S or A4b4/L1FR-S28R is administered intramuscularly to a cotton rat than when the same concentration of SYNAGIS® is administered intramuscularly to a cotton rat.

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### Materials & Methods

#### Intramuscular Cotton Rat Prophylaxis

Cotton rats (*S. hispidus*, average weight 100 grams) were anesthetized with methoxyflurane and dosed with 0.1 ml of purified monoclonal antibody (MAb) or BSA 5 control by intramuscular (i.m.) injection. Twenty-four hours later animals were again anesthetized, bled for serum MAb concentration determination, and challenged with  $10^5$  PFU RSV long by intranasal (i.n.) instillation. Four days later animals were sacrificed, serum samples were obtained, and their lungs were harvested. Lungs were homogenized in 10 parts (wt/vol) of Hanks Balanced Salt solution and the resultant suspension was used to 10 determine pulmonary viral titers by plaque assay.

#### Intramuscular Cotton Rat Pharmacokinetics

Cotton rats (*S. hispidus*, average weight 100 grams) were anesthetized with methoxyflurane and dosed with 0.1 ml of purified MAb or BSA control by intramuscular 15 (i.m) injection. Twenty-four hours later all of the animals were bled for serum MAb concentration determination, and half of the animals from each group were sacrificed to perform bronchoalveolar lavage (BAL). Four days later the remaining animals were sacrificed, serum samples were obtained and BAL performed.

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### Results

As shown in Tables 14-16, a greater reduction in RSV titer is achieved with equivalent or lower lung levels of A4b4, A4b4-F52S, or A4b4/L1FR-S28R as with SYNAGIS®.

25 Table 14: Intramuscular Cotton Rat Prophylaxis Data

|    | 0.5mg/kg          |                  |                      |                   | 0.125mg/kg        |                  |                      |                   |     |
|----|-------------------|------------------|----------------------|-------------------|-------------------|------------------|----------------------|-------------------|-----|
|    | Serum IgG (µg/ml) | Lung IgG (µg/ml) | Virus Titer (pfu/gm) | log Virus Titer   | Serum IgG (µg/ml) | Lung IgG (µg/ml) | Virus Titer (pfu/gm) | log Virus Titer   |     |
|    | Synagis           | 3.4              | 0.099                | $7.3 \times 10^3$ | 3.9               | 0.893            | 0.024                | $3.1 \times 10^4$ | 4.5 |
| 30 | A4b4-F52S         | 2.9              | 0.089                | $7.3 \times 10^2$ | 2.9               | 0.781            | 0.020                | $8.6 \times 10^3$ | 3.9 |
|    | A4b4/L1FR-S28R    | 3.3              | 0.093                | $6.1 \times 10^2$ | 2.8               | 0.748            | 0.016                | $2.3 \times 10^4$ | 4.4 |
|    | BSA               |                  |                      | $5.9 \times 10^4$ | 4.8               |                  |                      |                   |     |

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Table 15: Intramuscular Cotton Rat Prophylaxis Data

| Molecule | 0.5mg/kg           |                   |                       | 1mg/kg             |                   |                       |
|----------|--------------------|-------------------|-----------------------|--------------------|-------------------|-----------------------|
|          | Serum IgG<br>µg/ml | Lung IgG<br>µg/ml | log(10)<br>Lung Virus | Serum IgG<br>µg/ml | Lung IgG<br>µg/ml | log(10)<br>Lung Virus |
| A4b4     | 2.4                | 0.013             | 4.3                   | 3.1                | 0.094             | 3.4                   |
| Synagis  | 1.9                | 0.038             | 4.4                   | 4.2                | 0.212             | 3.3                   |
| BSA      |                    |                   |                       |                    |                   | 4.4                   |

Table 16: Intramuscular Cotton Rat Pharmacokinetics Data

| Molecule | 24 Hours             |                    | 96 hours             |                    |
|----------|----------------------|--------------------|----------------------|--------------------|
|          | Serum IgG<br>(µg/ml) | BAL IgG<br>(ng/ml) | Serum IgG<br>(µg/ml) | BAL IgG<br>(ng/ml) |
| A4b4     | 3.4                  | 2.2                | 2.6                  | 1.4                |
| Synagis  | 4.1                  | 5.3                | 2.8                  | 3.5                |

15        12.     **EXAMPLE: *IN VITRO* ISOLATION OF SYNAGIS® SPECIFIC  
MONOCLONAL ANTIBODY RESISTANT  
MUTANTS(MARM) OF RSV STRAIN A/ LONG**

This example demonstrates that MARMs can be isolated from RSV laboratory strain A/ Long upon multiple rounds of selection in the presence of SYNAGIS®.

20        **Materials:**

SYNAGIS® (formulated product: ref RN1002.148), Control Pan RSV MAb Pool (Chemicon MAB858-4, a blend of three MAbs anti-F, G, and N proteins), anti-RSV Type A MAb (Chemicon MAB858-1), and anti-RSV Type B MAb (Chemicon MAB858-2) were used in this study. Secondary detecting reagents were either Alexa™488 conjugated Goat F(ab')<sub>2</sub> anti- Mouse or Human IgG (H+L). RSV A/ Long strain (5x10<sup>7</sup> TCID<sub>50</sub>/ml) was propagated from Master Virus Bank 031797. HEp-2 cells were propagated in EMEM supplemented with 10% FBS and 2 mM L-Gln in a 37°C, 5% CO<sub>2</sub> environment. Total cellular RNAs were isolated from infected HEp-2 cells with the Promega RNaAgents Kit. cDNAs were synthesized with the Boehringer Mannheim 1<sup>st</sup> Strand cDNA Synthesis Kit, using Oligo- (dT) primer. Amplification of a fragment of the F protein for DNA sequencing was performed by Polymerase Chain Reaction (PCR), using gene-specific oligonucleotides (MR-120 and MR-122) and the Boehringer Mannheim High Fidelity PCR Kit.

**Methods:****Selection of MARMs:**

4 x 10<sup>5</sup> HEp-2 cells were seeded per well of a 24-well plate in growth medium (EMEM, 10% FBS, 2 mM L-Gln) and incubated overnight in growth conditions (37°C, 5% CO<sub>2</sub>). 40 wells were seeded for individual MARM selection. Prior to infection, a fresh vial of master virus bank RSV A/ Long was thawed rapidly at 37°C and the virus titer adjusted to 4x10<sup>6</sup> pfu/ml in HEp-2 growth medium. SYNAGIS® was added to the virus inoculum at a final concentration of 30 µg/ml, and the mixture was incubated at 37°C for one hour. An aliquot of RSV was incubated with an irrelevant Human IgG1 Mab (MEDI-507) and was used as a negative control. An uninfected control well was also set up for each plate. Cells were washed once with fresh medium and were overlayed with 100 µl of RSV A/ Long virus stock/MAb mixture (multiplicity of infection [m.o.i.] = 4). Cells were incubated for four hours in growth conditions followed by addition of 1 ml of growth medium to each well. Cytopathic effect (CPE) was monitored on a daily basis by light microscopy.

Following seven days of selection the contents of each well were supplemented with a further 30 µg/ml of SYNAGIS® or irrelevant Human IgG1 Mab, and were used to infect freshly seeded HEp-2 cells (4x10<sup>5</sup> cells/ well of 24-well plate). After a further seven days of selection the process was repeated one more time for a total of three rounds of selection.

**20 Plaque Purification of MARMs:**

After the third round of selection, the contents of ten independent wells were chosen at random and used for plaque purification of MARMs. The remaining supernatants were mixed 1:1 with 50% sucrose solution and immediately frozen at -80°C. Supernatants were diluted 1:10, 1:100, and 1:1000 in growth medium and incubated with 30 µg/ml of SYNAGIS® for one hour prior to infection. 1 ml of virus inoculum was overlayed on monolayers of HEp-2 cells in 60mm round culture dishes (1x10<sup>6</sup> cells/ dish) and incubated for 4 hours in growth conditions. Following infection the inoculum was carefully aspirated and cells were overlayed with 3 ml growth medium supplemented with 0.8% low melting temperature agarose (Gibco BRL), and containing 30 µg/ml of SYNAGIS®. Dishes were returned to the incubator after complete solidification of agarose and monitored daily for plaque formation. Uninfected controls and wild type RSV control plates were set up for comparison. After five to six days, each plate was overlayed with an additional 2 ml of 0.8% agarose in growth medium supplemented with 50 µg/ml neutral red. Following an overnight incubation in growth conditions, plaques were scored and picked for a second round of purification.

Amplification of clonal MARMs:

Following a second round of plaque purification two clones from each isolate were expanded for production of high titer viral stocks. Individual plaques were picked with the aid of a pipet tip and incubated in 0.1 ml of fresh medium at 4°C overnight to elute the virus. Each aliquot was used to infect HEp-2 cells in flat bottom 96-well plates ( $1 \times 10^4$  cells/ well) in the presence of 30  $\mu$ g/ml SYNAGIS®. After five days the entire well content was used to infect HEp-2 cells in the presence of 30  $\mu$ g/ml of SYNAGIS® in 24-well plates. Each inoculum was subsequently expanded in the presence of 30  $\mu$ g/ml of SYNAGIS® to a T-25 flask ( $1 \times 10^6$  cells/ flask) and 5 mls of high titer virus stock were produced. MARM stocks were frozen as described above.

F protein cDNA synthesis and DNA sequencing:

In order to determine the nucleotide sequence of an approximately 400 nucleotide region of the F protein gene thought to contain the epitope for SYNAGIS®, First strand cDNA synthesis was performed with total cellular RNAs isolated from MARM-infected HEp-2 cells at 4 days post-infection. Amplification of a fragment of the F protein for DNA sequencing was performed as described in Materials section. Amplified MARM F-protein cDNAs were purified by phenol/chloroform extraction and ethanol precipitation, and used in a PCR sequencing reaction with gene-specific oligos and Perkin-Elmer Cetus Big-Dye Terminator reaction mix to sequence the relevant region.

Immunofluorescence Assay (IFA):

Cells infected with RSV isolates were tested for anti-RSV binding by SYNAGIS® and Control Pan RSV MAb Pool, as follows. Four to five day RSV-infected HEp-2 cultures were mixed with PBS and centrifuged at 300xg for 5 minutes at room temperature. Pellets were resuspended in a small volume of PBS for analysis. Five to ten microliters of each cell suspension were spotted per 5 mm well on acetone washed 12-well HTC super cured glass slides and allowed to air dry. Slides were fixed in cold (-20°C) acetone for 10 minutes. Reactions were blocked by spotting 10  $\mu$ l of 1% BSA in PBS into each well and incubating for 10 minutes at room temperature. Slides were washed three times in 1X PBS/ 0.1% Tween-20 and air-dried. Ten microliters of each primary antibody reagent diluted to 250 ng/ml in blocking buffer were spotted per well and reactions were incubated in a humidified 37°C environment for 30 minutes. Slides were then washed for 1 minute in three changes of 1X PBS/ 0.1% Tween-20 and were air-dried. Ten microliters of appropriate secondary conjugated antibody reagent diluted to 250 ng/ml in blocking buffer were added to each

respective well and reactions were incubated in a humidified 37°C environment for an additional 30 minutes. Slides were then washed for 1 minute in three changes of 1X PBS/ 0.1% Tween-20. Five micro liters of 50% glycerol in PBS, 10 mM Tris, pH 8.0, 1 mM EDTA were spotted in each reaction well, and slides were mounted with cover slips. Each 5 reaction well was subsequently analyzed by fluorescence microscopy at 200X power using a B-2A filter (EX 450-490 nm). Positive reactions were scored against an auto-fluorescent background obtained with unstained cells or cells stained with secondary reagent alone.

RSV positive reactions were characterized by bright fluorescence punctuated with small inclusions in the cytoplasm of infected cells.

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Microneutralization Assay:

The procedure used here is described in Johnson et al., 1999, J. Infectious Diseases 180:35-40, the disclosure of which is hereby incorporated by reference in its entirety. Briefly, antibody dilutions were made in triplicate using a 96-well plate. Ten TCID<sub>50</sub> of 15 RSV A MARMS were incubated with serial dilutions of the antibody to be tested for 2 hours at 37°C in the wells of a 96-well plate. The antibodies used in the assay comprised the heavy chain of SYNAGIS®, the heavy chain of SYNAGIS® with a point mutation or the heavy chain of A4B4, and the light chain of SYNAGIS®, the light chain of SYNAGIS® with point mutations, the light chain of A4B4 with point mutations, the light chain of A4B4 20 with point mutations, the light chain of L1FR (a.k.a. 1X-493L1FR) or the light chain of L1FR with point mutations. Mab 13/19 was used in the assay as a positive control. RSV susceptible HEp-2 cells (2.5 x 10<sup>4</sup>) were then added to each well and cultured for 5 days at 37°C in 5% CO<sub>2</sub>. After 5 days, the medium was aspirated and cells were washed and fixed to the plates with 80% methanol and 20% PBS. RSV replication was then determined by F 25 protein expression. Fixed cells were incubated with a biotin-conjugated anti-F protein monoclonal antibody (pan F protein, C-site-specific MAb 133-1H) washed and horseradish peroxidase conjugated avidin was added to the wells. The wells were washed again and turnover of substrate TMB (thionitrobenzoic acid) was measured at 450 nm. The results from the assay for the monoclonal antibodies are shown in Table 19 *infra*.

30

Results and Discussion:

The binding activity of SYNAGIS® was tested by IFA against a panel of 20 RSV A/ Long MARMS obtained by three rounds of selection on HEp-2 cells in the presence of SYNAGIS®. A pool of monoclonal antibodies against the fusion, glycoprotein, and nuclear 35 proteins of RSV (Control Pan RSV MAb Pool) was used as a positive control for detection

of RSV. Subtyping of RSV MARMs was performed with two monoclonal antibodies that distinguish type A and type B glycoproteins. As summarized in Table 17, lack of binding activity by SYNAGIS® was demonstrated in all 20 MARMs. Contrasting with lack of binding by SYNAGIS®, binding of the Control Pan RSV MAb Pool was demonstrated for 5 all MARMs tested. All 20 MARMs were classified as RSV type A. Wild type RSV A/ Long infected HEp-2 cells bound SYNAGIS®, Pan RSV MAb Pool, and RSV Type A MAb, but failed to react with RSV Type B MAb, as expected.

DNA sequencing analysis of an approximately 400-nucleotide region of the RSV F protein cDNA encompassing the proposed SYNAGIS® epitope revealed a single mutation at 10 the amino-acid level at position 272. Table 18 shows the amino acid change at position 272 in twelve isolates sequenced to date. Although the entire nucleotide sequence of RSV MARMs F protein has not been determined, these results suggest that amino acid 272 is a critical residue in modulating the binding of SYNAGIS® to its epitope.

The ability of various monoclonal antibodies to neutralize the replication of RSV A 15 MARMs was determined. As shown in Table 19, the ability of the monoclonal antibodies to neutralize the replication of RSV MARMs varied depending upon the amino acid sequence of the heavy chain (HC) and light chain (LC) of the antibody.

20 Table 17. Characterization of anti-RSV Binding Activity by SYNAGIS®, Control Pan RSV MAb Pool (anti-F, G, N proteins), anti-RSV Type A MAb, and anti-RSV Type B MAb by Immunofluorescence Assay (IFA) on RSV A/ Long MARMs.

| RSV MARM | Reactivity w/<br>SYNAGIS® | Reactivity w/<br>anti-RSV MAb Pool | Reactivity w/<br>anti-RSV type A MAb | Reactivity w/<br>Anti-RSV type B MAb |
|----------|---------------------------|------------------------------------|--------------------------------------|--------------------------------------|
| B1       | -                         | +                                  | +                                    | -                                    |
| B2       | -                         | +                                  | +                                    | -                                    |
| B3       | -                         | +                                  | +                                    | -                                    |
| B4       | -                         | +                                  | +                                    | -                                    |
| B5       | -                         | +                                  | +                                    | -                                    |
| B6       | -                         | +                                  | +                                    | -                                    |
| B7       | -                         | +                                  | +                                    | -                                    |
| B8       | -                         | +                                  | +                                    | -                                    |
| B9       | -                         | +                                  | +                                    | -                                    |
| B10      | -                         | +                                  | +                                    | -                                    |
| B11      | -                         | +                                  | +                                    | -                                    |
| B12      | -                         | +                                  | +                                    | -                                    |
| B13      | -                         | +                                  | +                                    | -                                    |
| B14      | -                         | +                                  | +                                    | -                                    |
| B15      | -                         | +                                  | +                                    | -                                    |
| B16      | -                         | +                                  | +                                    | -                                    |
| B17      | -                         | +                                  | +                                    | -                                    |
| B18      | -                         | +                                  | +                                    | -                                    |

|           |   |   |   |   |
|-----------|---|---|---|---|
| B19       | - | + | + | - |
| B20       | - | + | + | - |
| Wt RSV A/ | + | + | + | - |

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Table 18. Amino acid sequence of a region of the wild type RSV A/ Long and MARMs F Protein encompassing the proposed SYNAGIS® epitope.

| Isolate            | Amino Acid Sequence (Position number) |     |     |     |     |     |     |     |     |     |     |     |     |     |
|--------------------|---------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                    | 266                                   | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 | 277 | 278 | 279 |
| Wild type RSV Long | I                                     | T   | N   | D   | Q   | K   | K   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B1            | I                                     | T   | N   | D   | Q   | K   | N   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B2            | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B3            | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B4            | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B6            | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B7            | I                                     | T   | N   | D   | Q   | K   | T   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B8            | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B9            | I                                     | T   | N   | D   | Q   | K   | Q   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B10           | I                                     | T   | N   | D   | Q   | K   | T   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B13           | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B14           | I                                     | T   | N   | D   | Q   | K   | Q   | L   | M   | S   | N   | N   | V   | Q   |
| MARM B15           | I                                     | T   | N   | D   | Q   | K   | M   | L   | M   | S   | N   | N   | V   | Q   |

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Table 19. MARM analysis by Microneutralization Assay

| RSV Microneutralization Assay On RSV A MARMs to Synagis with RSV Monoclonal Antibody |                      | MARMs to SYNAGIS® |       |       |       | Note        |
|--|----------------------|-------------------|-------|-------|-------|-------------|
| Amino Acid Change  | Antibody             | K272Q             | K272N | K272M | K272T |             |
| HC/LC  | SYNAGIS®/SYNAGIS®    | -                 | -     | -     | -     | Purified Ab |
| A4B4/A4B4  | A4B4/SYNAGIS®        | +                 | +     | +     | +     | Purified Ab |
|  | SYNAGIS®/A4B4        | +                 | +     | +     | -     | Purified Ab |
| A4B4/L1FR  | A4B4/L1FR S28R       | -                 | -     | -     | -     | Purified Ab |
| A4B4/L1FR S28R, S52F   | A4B4/L1FR S28R, S52F | +                 | +     | +     | +     | Purified Ab |
| A4B4/L1FR-28R, S2F, F93  | A4B4/A4b428S         | -                 | -     | -     | -     | Purified Ab |
| A4B4/A4b452S   | A4B4/A4b452S         | +                 | +     | +     | +     | Purified Ab |
| Mab 13/19  | SYNAGIS®/K53F        | +                 | +     | +     | +     | Purified Ab |
| SYNAGIS®/S28R  | SYNAGIS®/Q26S        | -                 | -     | -     | -     | 293H sup    |
| SYNAGIS®/A55D  | SYNAGIS®/K24S        | -                 | -     | -     | -     | 293H sup    |
| SYNAGIS®/C25A  | SYNAGIS®/L27S        | -                 | -     | -     | -     | 293H sup    |

|                |   |   |             |
|----------------|---|---|-------------|
| SYNAGIS®/SS2F  | - | - | 293H sup    |
| SYNAGIS®/L105V | - | - | 293H sup    |
| T98F/SYNAGIS®  | - | - | Purified ab |
| S32A/SYNAGIS®  | - | - | 293H sup    |
| S95D/SYNAGIS®  | - | - | 293H sup    |
| D58H/SYNAGIS®  | - | - | 293H sup    |
| A105Q/SYNAGIS® | - | - | 293H sup    |
| S65D/SYNAGIS®  | - | - | 293H sup    |
| W100F/SYNAGIS® | - | - | 293H sup    |

+= neutralization detected; - = no neutralization detected

13. EXAMPLE: ***IN VITRO ISOLATION OF A4B4 SPECIFIC  
MONOCLONAL ANTIBODY RESISTANT  
MUTANTS (MARM) OF RSV STRAIN A/ LONG***

This example demonstrates that MARMs can be isolated from RSV laboratory strain A/ Long upon multiple rounds of selection in the presence of A4B4

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**Materials:**

A4B4 (Lot # 524-9, 3.57 mg /ml), Control Pan RSV MAb Pool (Chemicon MAB858-4, a blend of three MAbs anti-F, G, and N proteins), anti-RSV Type A MAb (Chemicon MAB858-1), and anti-RSV Type B MAb (Chemicon MAB858-2) were used in this study. Secondary detecting reagents were either Alexa<sup>TM</sup>488 conjugated Goat F (ab'), anti- Mouse or Human IgG (H+L). Virus bank of RSV A/ Long strain NWVB020500 (2.38x10<sup>7</sup> TCID<sub>50</sub>/ml) propagated from Master Virus Bank 031797. HEp-2 cells were propagated in EMEM supplemented with 10% FBS and 2 mM L-Gln in a 37°C, 5% CO<sub>2</sub> environment. Messenger RNA was purified from the infected cells using the mRNA Capture Kit (Roche). The mRNA samples were used to make cDNA using the reagents from the cDNA First Strand Reacition Kit (Roche), followed by amplification of the RSV F protein gene by the Polymerase Chain Reaction (PCR) using gene specific primers.

20

**Methods:**

**Selection of MARMs:**

4 x 10<sup>5</sup> HEp-2 cells were seeded per well of a 24-well plate in growth medium (EMEM, 10% FBS, 2 mM L-Gln) and incubated overnight in growth conditions (37°C, 5% CO<sub>2</sub>). 44 wells were seeded for individual MARM selection. Prior to infection, a fresh vial of virus bank RSV A/ Long was thawed rapidly at 37°C and the virus titer adjusted to 4x10<sup>6</sup> pfu/ml in HEp-2 growth medium. A4B4 was added to the virus inoculum at a final concentration of 2 µg/ml, and the mixture was incubated at 37°C for one hour. An aliquot of RSV was incubated with an irrelevant Human IgG1 Mab (MEDI-507) and was used as a negative control. An uninfected control well was also set up for each plate. Cells were washed once with fresh medium and were overlayed with 100 µl of RSV A/ Long virus stock/MAb mixture. Cells were incubated for four hours in growth conditions followed by addition of 1 ml of growth medium to each well. Cytopathic effect (CPE) was monitored on a daily basis by light microscopy. Following seven days of selection the contents of each well were supplemented with a further 4 µg/ml of A4B4 or irrelevant Human IgG1 Mab, and were used to infect freshly seeded HEp-2 cells (4x10<sup>5</sup> cells/ well of 24-well plate). After a further seven days of selection the process was repeated one more time for a total of

three rounds of selection. The contents of wells showing clear CPE were mixed 1:1 with 50% sucrose solution and immediately frozen at -80°C

Plaque Purification of MARMs:

5 After the third round of selection, the contents of two independent wells were chosen at random and used for plaque purification of MARMs. A fresh vial of MARM stock (was frozen after third round of selection) was thawed at room temperature and was diluted 1:10, 1:100, and 1:1000 in growth medium and incubated with 4 µg/ml of A4B4 for one hour prior to infection. 0.5 ml of virus inoculum was overlayed on monolayers of HEp-10 2 cells in 6 well plates ( $5 \times 10^5$  cells/ well) and incubated for 4 hours in growth conditions. Following infection the inoculum was carefully aspirated and cells were overlayed with 2 ml growth medium supplemented with 0.8% low melting temperature agarose (Gibco BRL), and containing 4 µg/ml of A4B4. Dishes were returned to the incubator after complete solidification of agarose and monitored daily for plaque formation. Uninfected controls and 15 wild type RSV control plates were set up for comparison. After five to six days, each plate was overlayed with an additional 2 ml of 0.8% agarose in growth medium supplemented with 50 µg/ml neutral red. Following an overnight incubation in growth conditions, plaques were scored and picked for a second round of purification.

20 Amplification of clonal MARMs:

Following a second round of plaque purification three clones from each isolate were expanded for production of high titer viral stocks. Individual plaques were picked with the aid of a pipet tip and incubated in 0.2 ml of fresh medium at 4°C overnight to elute the virus. Each aliquot was used to infect HEp-2 cells in flat bottom 24-well plates ( $2.5 \times 10^5$  cells/ well- seeded day before) in the presence of 4 µg/ml A4B4. After five days the entire well content was used to infect HEp-2 cells in the presence of 4 µg/ml of A4b4 in 24-well plates. Each inoculum was subsequently expanded in the presence of 4 µg/ml of A4b4 to a T-25 flask ( $6.5 \times 10^5$  cells/ flask – seeded day before) and 5 mls of high titer virus stock were produced. MARM stocks were frozen as described above.

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F protein cDNA synthesis and DNA sequencing:

In order to determine the nucleotide sequence of an approximately 800 nucleotide region of the F protein gene thought to contain the epitope for SYNAGIS®, First strand cDNA synthesis was performed with mRNAs isolated from MARM-infected HEp-2 cells at 35 4 days post-infection. RSV infected Hep2 cells were lysed in 150 µl of lysis buffer

provided with the mRNA capture kit. Biotinylated oligo dT was diluted 1:10 with nuclease free H<sub>2</sub>O and 4  $\mu$ l was added to each lysate. Samples were incubated 10 minutes at 42°C to allow the oligo dT to anneal to the mRNA. A 50  $\mu$ l aliquot of the lysate was transferred to a streptavidin coated PCR tube and incubated for three minutes at 37°C. The lysates were 5 removed from the PCR tubes and discarded. The RNA captured in the tubes was washed three times with 200  $\mu$ l of wash buffer.

RT reactions were performed using reagents from the First Strand cDNA kit (Roche Molecular Biochemicals). A master mix was prepared so that each reaction contained 5  $\mu$ l 10 X buffer, 5  $\mu$ l dNTPs, 10  $\mu$ l MgCl<sub>2</sub>, 1  $\mu$ l gelatin, 2  $\mu$ l RNase Inhibitor, 2  $\mu$ l AMV-RT, in 10 a final volume of 50  $\mu$ l. Fifty microliter aliquots of the master mix were transferred to the PCR tubes containing the captured mRNA. Samples were placed in a thermalcycler and incubated for two hours at 42°C. The cDNA reaction mix was then removed from the PCR tubes and discarded. The cDNA captured in the PCR tubes was washed with 200  $\mu$ l of wash buffer To obtain enough of the RSV F protein gene for sequence analysis, the cDNA 15 was subjected to PCR using gene specific primers. Each reactions contained 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 2.5 mM MgCl<sub>2</sub>, 200  $\mu$ M dNTPs, 125 ng of each forward (5'AGTGTCTAACCAAGCAGTAGTGTAGA 3'; SEQ ID NO:258) and reverse (5' TCATTGACTTGAGATATTGATGCATC 3'; SEQ ID NO:259) primer, and 2.5 units of Taq polymerase (PE Biosystems) in a final volume of 50  $\mu$ l. The temperature profile for all 20 reactions was 95°C for 2 min, followed by 40 cycles of 95°C for 30 sec., 55°C for 45 sec, 72°C for 45 sec, with a final extension at 72°C for 10 minutes.

All PCR products were separated by electrophoresis on a 2% agarose gel in 1X TBE and visualized by ethidium bromide fluorescence.

PCR products were purified using Qiaquick spin columns (Qiagen and sequenced 25 using the Big Dye-terminator PRISM kit (Applied Biosystems (ABI)). The reactions contained 70 ng of PCR product as template, 3 pmols of primer, and 8.0  $\mu$ l of the PRISM dye-terminator reaction mix in a final volume of 20  $\mu$ l. The reactions were subjected to thermal cycling according to ABI's dye-terminator sequencing instructions. Unincorporated dyes were removed from the extension products using Centri-Sep spin columns (Princeton 30 Separations). Extension products were dried in a Savant Speed Vac and then dissolved in 10  $\mu$ l HiDi Formamide (ABI) loading buffer. Samples were applied by electrophoresis in an ABI 3100 automated sequencer. Sequence data collected by the sequencer was analyzed using Lasargene (DNA Star).

Immunofluorescence Assay (IFA):

Cells infected with RSV isolates were tested for anti-RSV binding by A4B4, SYNAGIS® and Control Pan RSV MAb Pool, as follows. Four to five day RSV-infected HEp-2 cultures were mixed with PBS and centrifuged at 300xg for 5 minutes at room temperature. Pellets were resuspended in a small volume of PBS for analysis. Five to ten micro liters of each cell suspension were spotted per 5 mm well on acetone washed 12-well HTC supercured glass slides and allowed to air dry. Slides were fixed in cold (-20°C) acetone for 10 minutes. Reactions were blocked by spotting 10 µl of 1% BSA in PBS into each well and incubating for 10 minutes at room temperature. Slides were washed three times in 1X PBS/ 0.1% Tween-20 and air-dried. Ten micro liters of each primary antibody reagent diluted to 250 ng/ml in blocking buffer were spotted per well and reactions were incubated in a humidified 37°C environment for 30 minutes. Slides were then washed for 1 minute in three changes of 1X PBS/ 0.1% Tween-20 and were air-dried. Ten micro liters of appropriate secondary conjugated antibody reagent diluted to 250 ng/ml in blocking buffer were added to each respective well and reactions were incubated in a humidified 37°C environment for an additional 30 minutes. Slides were then washed for 1 minute in three changes of 1X PBS/ 0.1% Tween-20. Five micro liters of 50% glycerol in PBS, 10 mM Tris, pH 8.0, 1 mM EDTA were spotted in each reaction well, and slides were mounted with cover slips. Each reaction well was subsequently analyzed by fluorescence microscopy at 200X power using a B-2A filter (EX 450-490 nm). Positive reactions were scored against an auto fluorescent background obtained with unstained cells or cells stained with secondary reagent alone.

RSV positive reactions were characterized by bright fluorescence punctuated with small inclusions in the cytoplasm of infected cells.

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Microneutralization Assay:

The procedure used here is described in Johnson et al., 1999, J. Infectious Diseases 180:35-40, the disclosure of which is hereby incorporated by reference in its entirety. Briefly, antibody dilutions were made in triplicate using a 96-well plate. Ten TCID<sub>50</sub> of RSV A MARMS were incubated with serial dilutions of the antibody to be tested for 2 hours at 37°C in the wells of a 96-well plate. The antibodies used in the assay comprised the heavy and light chain of SYNAGIS®, the heavy and light chain of A4b4, the combination of the heavy and light chain of SYNAGIS® and A4b4, the SYNAGIS® heavy chain or light chain with a point mutation in light chain or heavy chain, or A4b4 heavy chain with point mutations in light chain. Mab 13/19 was used as a positive control in the

assay. RSV susceptible HEp-2 cells ( $2.5 \times 10^4$ ) were then added to each well and cultured for 5 days at 37°C in 5% CO<sub>2</sub>. After 5 days, the medium was aspirated and cells were washed and fixed to the plates with 80% methanol and 20% PBS. RSV replication was then determined by F protein expression. Fixed cells were incubated with a biotin-conjugated 5 anti-F protein monoclonal antibody (pan F protein, C-site-specific MAAb 133-1H) washed and horseradish peroxidase conjugated avidin was added to the wells. The wells were washed again and turnover of substrate TMB (thionitrobenzoic acid) was measured at 450 nm. The results from the assay for the monoclonal antibodies are shown in Table 22 *infra*.

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#### Results and Discussion:

The binding activity of A4B4 was tested by IFA against a panel of RSV A/ Long MARMs obtained by three rounds of selection on HEp-2 cells in the presence of SYNAGIS®. A pool of monoclonal antibodies against the fusion, glycoprotein, and nuclear proteins of RSV (Control Pan RSV MAAb Pool) was used as a positive control for detection 15 of RSV. Subtyping of RSV MARMs was performed with two monoclonal antibodies that distinguish type A and type B glycoproteins. As summarized in Table 20, lack of binding activity by A4B4 and SYNAGIS® was demonstrated in MARMs. Contrasting with lack of binding by A4B4 and SYNAGIS®, binding of the Control Pan RSV MAAb Pool was demonstrated for all MARMs tested. Both MARMs were classified as RSV type A. Wild 20 type RSV A/ Long infected HEp-2 cells bound to A4B4 and SYNAGIS®, Pan RSV MAAb Pool, and RSV Type A MAAb, but failed to react with RSV Type B MAAb, as expected.

DNA sequencing analysis of an approximately 800-nucleotide region of the RSV F protein cDNA encompassing the proposed A4B4 epitope revealed mutation at the amino-acid level at position 272 and 276. Table 21 shows the amino acid change in isolates 25 sequenced to date. Although the entire nucleotide sequence of RSV MARMs F protein has not been determined, these results suggest that amino acid 272 and 276 is a critical residue in modulating the binding of A4B4 to its epitope.

The ability of various monoclonal antibodies to neutralize the replication of a RSV A MARM was determined. As shown in Table 22, the ability of the monoclonal antibodies 30 to neutralize the replication of a RSV MARM varied depending upon the amino acid sequence of the heavy chain (HC) and light chain (LC) of the antibody.

Table 20. Characterization of anti-RSV Binding Activity by A4B4, Synagis®, Control Pan RSV MAb Pool (anti-F, G, N proteins), anti-RSV Type A MAb, and anti-RSV Type B MAb by Immunofluorescence Assay (IFA) on RSV A/ Long MARMs.

| RSV MARM sample | Reactivity w/<br>Synagis® |   | Reactivity w/<br>Anti-RSV MAb Pool |   | Reactivity w/<br>Anti-RSV Type A MAb |   | Reactivity w/<br>Anti-RSV Type B MAb |   | Reactivity<br>A4B4 |
|-----------------|---------------------------|---|------------------------------------|---|--------------------------------------|---|--------------------------------------|---|--------------------|
|                 | +                         | - | +                                  | - | +                                    | - | +                                    | - |                    |
| MARM #6         | -                         | + | -                                  | + | -                                    | - | -                                    | - | -                  |
| MARM #9         | -                         | + | -                                  | + | -                                    | - | -                                    | - | -                  |
| MARM #10        | -                         | + | -                                  | + | -                                    | - | -                                    | - | -                  |
| MARM #11        | -                         | + | -                                  | + | -                                    | - | -                                    | - | -                  |
| Wt              | +                         | + | +                                  | + | -                                    | - | -                                    | - | +                  |

Table 21. Amino acid sequence of a region of the wild type RSV A/ Long and MARMs F Protein.

| Isolate       | Amino Acid Sequence (Position number) |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------|---------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|               | 266                                   | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 | 277 | 278 | 279 |
| Wild type RSV | I                                     | T   | N   | D   | Q   | K   | K   | L   | M   | S   | N   | N   | V   | Q   |
| MARM #10      | I                                     | T   | N   | D   | Q   | K   | E   | L   | M   | S   | Y   | N   | V   | Q   |
| MARM #6       | I                                     | T   | N   | D   | Q   | K   | E   | L   | M   | S   | N   | N   | V   | Q   |
| MARM #9       | I                                     | T   | N   | D   | Q   | K   | E   | L   | M   | S   | N   | N   | V   | Q   |
| MARM #11      | I                                     | T   | N   | D   | Q   | K   | E   | L   | M   | S   | N   | N   | V   | Q   |
| MARM #14      | I                                     | T   | N   | D   | Q   | K   | E   | L   | M   | S   | N   | N   | V   | Q   |

Table 22. MARM analysis by Microneutralization Assay

| RSV Microneutralization Assay On RSV A MARMs to<br>A4B4 with RSV Monoclonal Antibody |                         |              |             |
|--|-------------------------|--------------|-------------|
|  |                         | K272E, N276Y |             |
|  | Antibody                | MARM to      | Note        |
|  | HC/LC                   | MARM 10      |             |
| 5  | SYNAGIS®/SYNAGIS®       | -            | Purified Ab |
| 10   | A4B4/A4B4               | -            | Purified Ab |
|  | A4b4/SYNAGIS®           | -            | Purified Ab |
| 15   | SYNAGIS®/A4B4           | -            | Purified Ab |
|  | A4B4/L1FR               | -            | Purified Ab |
|  | A4B4/L1FR S28R          | -            | Purified Ab |
|  | A4B4/L1FR S28R, S52F    | -            | Purified Ab |
|  | A4B4/L1FR-28R, 52F, 93F | -            | Purified Ab |
|  | A4B4/A4B428S            | -            | Purified Ab |
|  | A4B4/A4B452S            | -            | Purified Ab |
|  | Mab 13/19               | +            | Purified Ab |

+ = neutralization detected; - = no neutralization detected

20 14. EXAMPLE: IN VITRO ISOLATION OF A4B4 SPECIFIC  
MONOCLONAL ANTIBODY RESISTANT  
MUTANTS (MARM) OF MARM B9( MARM OF RSV  
STRAIN A/ LONG TO SYNAGIS)

25 This example demonstrates that MARMs can be isolated from MARM of RSV A long to Synagis (MARM B9) upon multiple rounds of selection in the presence of A4B4

30 25 Materials:  
A4B4 (Lot # 524-9, 3.57 mg /ml), Control Pan RSV MAb Pool (Chemicon MAB858-4, a blend of three Mabs anti-F, G, and N proteins), anti-RSV Type A MAb (Chemicon MAB858-1), and anti-RSV Type B MAb (Chemicon MAB858-2) were used in this study. Secondary detecting reagents were either Alexa™488 conjugated Goat F (ab')<sub>2</sub> anti- Mouse or Human IgG (H+L). MARM B9 (1.78x10<sup>6</sup> TCID<sub>50</sub>/ml) was used here. HEp-2 cells were propagated in EMEM supplemented with 10% FBS and 2 mM L-Gln in a 37°C, 5% CO<sub>2</sub> environment. Messenger RNA was purified from the infected cells using the mRNA Capture Kit (Roche). The mRNA samples were used to make cDNA using the reagents from the cDNA First Strand Reacition Kit (Roche), followed by amplification of

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the RSV F protein gene by the Polymerase Chain Reaction (PCR) using gene specific primers.

**Methods:**

5 **Selection of MARMs:**

4 x 10<sup>5</sup> HEp-2 cells were seeded per well of a 24-well plate in growth medium (EMEM, 10% FBS, 2 mM L-Gln) and incubated overnight in growth conditions (37°C, 5% CO<sub>2</sub>). 44 wells were seeded for individual MARM selection. Prior to infection, a fresh vial of virus bank MARM B9 was thawed rapidly at 37°C and the virus titer adjusted to 6x10<sup>5</sup> pfu/ml in HEp-2 growth medium. A4B4 was added to the virus inoculum at a final concentration of 2 µg/ml, and the mixture was incubated at 37°C for one hour. An aliquot of RSV was incubated with an irrelevant Human IgG1 Mab (MEDI-507) and was used as a negative control. An uninfected control well was also set up for each plate. Cells were washed once with fresh medium and were overlayed with 100 µl of RSV A/ Long virus stock/MAb mixture. Cells were incubated for four hours in growth conditions followed by addition of 1 ml of growth medium to each well. Cytopathic effect (CPE) was monitored on a daily basis by light microscopy. Following seven days of selection the contents of each well were supplemented with a further 4 µg/ml of A4B4 or irrelevant Human IgG1 Mab, and were used to infect freshly seeded HEp-2 cells (4x10<sup>5</sup> cells/ well of 24-well plate).

10 After a further seven days of selection the process was repeated one more time for a total of three rounds of selection. The contents of wells showing clear CPE were mixed 1:1 with 50% sucrose solution and immediately frozen at -80°C

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**Plaque Purification of MARMs:**

20 After the third round of selection, the contents of independent wells were used for plaque purification of MARMs. A fresh vial of MARM stock (was frozen after third round of selection) was thawed at room temperature and was diluted 1:10, 1:100, and 1:1000 in growth medium and incubated with 4 µg/ml of A4B4 for one hour prior to infection. 0.5 ml of virus inoculum was overlayed on monolayers of HEp-2 cells in 6 well plates (5x10<sup>5</sup> cells/ well) and incubated for 4 hours in growth conditions. Following infection the inoculum was carefully aspirated and cells were overlayed with 2 ml growth medium supplemented with 0.8% low melting temperature agarose (Gibco BRL), and containing 4 µg/ml of A4B4. Dishes were returned to the incubator after complete solidification of agarose and monitored daily for plaque formation. Uninfected controls and MARM B9 RSV control plates were set up for comparison. After five to six days, each plate was overlayed with an additional 2

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ml of 0.8% agarose in growth medium supplemented with 50 µg/ml neutral red. Following an overnight incubation in growth conditions, plaques were scored and picked for a second round of purification.

5 Amplification of clonal MARMs:

Following a second round of plaque purification three clones from isolate were expanded for production of high titer viral stocks. Individual plaques were picked with the aid of a pipet tip and incubated in 0.2 ml of fresh medium at 4°C overnight to elute the virus. Each aliquot was used to infect HEp-2 cells in flat bottom 24-well plates ( $2.5 \times 10^5$  cells/ well- seeded day before) in the presence of 4 µg/ml A4B4. After five days the entire well content was used to infect HEp-2 cells in the presence of 4 µg/ml of A4B4 in 24-well plates. Each inoculum was subsequently expanded in the presence of 4 µg/ml of A4B4 to a T-25 flask ( $6.5 \times 10^5$  cells/ flask – seeded day before) and 5 mls of high titer virus stock were produced. MARM stocks were frozen as described above.

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F protein cDNA synthesis and DNA sequencing:

In order to determine the nucleotide sequence of an approximately 800 nucleotide region of the F protein gene thought to contain the epitope for SYNAGIS®, First strand cDNA synthesis was performed with mRNAs isolated from MARM-infected HEp-2 cells at 20 4 days post-infection. RSV infected Hep2 cells were lysed in 150 µl of lysis buffer provided with the mRNA capture kit. Biotinylated oligo dT was diluted 1:10 with nuclease free H<sub>2</sub>O and 4 µl was added to each lysate. Samples were incubated 10 minutes at 42°C to allow the oligo dT to anneal to the mRNA. A 50 µl aliquot of the lysate was transferred to a streptavidin coated PCR tube and incubated for three minutes at 37°C. The lysates were 25 removed from the PCR tubes and discarded. The RNA captured in the tubes was washed three times with 200 µl of wash buffer.

RT reactions were performed using reagents from the First Strand cDNA kit (Roche Molecular Biochemicals). A master mix was prepared so that each reaction contained 5 µl 10 X buffer, 5 µl dNTPs, 10 µl MgCl<sub>2</sub>, 1µl gelatin, 2 µl RNase Inhibitor, 2 µl AMV-RT, in 30 a final volume of 50 µl. Fifty microliter aliquots of the master mix were transferred to the PCR tubes containing the captured mRNA. Samples were placed in a thermalcycler and incubated for two hours at 42 °C. The cDNA reaction mix was then removed from the PCR tubes and discarded. The cDNA captured in the PCR tubes was washed with 200 µl of wash buffer To obtain enough of the RSV F protein gene for sequence analysis, the cDNA 35 was subjected to PCR using gene specific primers. Each reactions contained 10 mM Tris-

HCl, pH 8.3, 50 mM KCl, 2.5 mM MgCl<sub>2</sub>, 200 μM dNTPs, 125 ng of each forward (5'AGTGTCTAACCAAGCAGAAAGTGTAGA 3'; SEQ ID NO:258) and reverse (5'TCATTGACTTGAGATATTGATGCATC 3'; SEQ ID NO:259) primer, and 2.5 units of Taq polymerase (PE Biosystems) in a final volume of 50 μl. The temperature profile for all 5 reactions was 95°C for 2 min, followed by 40 cycles of 95°C for 30 sec., 55°C for 45 sec, 72°C for 45 sec, with a final extension at 72°C for 10 minutes.

All PCR products were separated by electrophoresis on a 2% agarose gel in 1X TBE and visualized by ethidium bromide fluorescence.

PCR products were purified using Qiaquick spin columns (Qiagen and sequenced 10 using the Big Dye-terminator PRISM kit (Applied Biosystems (ABI)). The reactions contained 70 ng of PCR product as template, 3 pmols of primer, and 8.0 μl of the PRISM dye-terminator reaction mix in a final volume of 20 μl. The reactions were subjected to thermal cycling according to ABI's dye-terminator sequencing instructions. Unincorporated dyes were removed from the extension products using Centri-Sep spin columns (Princeton 15 Separations). Extension products were dried in a Savant Speed Vac and then dissolved in 10 μl HiDi Formamide (ABI) loading buffer. Samples were applied by electrophoresis in an ABI 3100 automated sequencer. Sequence data collected by the sequencer was analyzed using Lasargene (DNA Star).

20 Immunofluorescence Assay (IFA):

Cells infected with RSV isolates were tested for anti-RSV binding by A4B4, SYNAGIS®, and Control Pan RSV MAbs, as follows. Four to five day RSV-infected HEp-2 cultures were mixed with PBS and centrifuged at 300xg for 5 minutes at room temperature. Pellets were resuspended in a small volume of PBS for analysis. Five to ten 25 micro liters of each cell suspension were spotted per 5 mm well on acetone washed 12-well HTC super cured glass slides and allowed to air dry. Slides were fixed in cold (-20°C) acetone for 10 minutes. Reactions were blocked by spotting 10 μl of 1% BSA in PBS into each well and incubating for 10 minutes at room temperature. Slides were washed three times in 1X PBS/ 0.1% Tween-20 and air-dried. Ten micro liters of each primary antibody 30 reagent diluted to 250 ng/ml in blocking buffer were spotted per well and reactions were incubated in a humidified 37°C environment for 30 minutes. Slides were then washed for 1 minute in three changes of 1X PBS/ 0.1% Tween-20 and were air-dried. Ten micro liters of appropriate secondary conjugated antibody reagent diluted to 250 ng/ml in blocking buffer were added to each respective well and reactions were incubated in a humidified 37°C 35 environment for an additional 30 minutes. Slides were then washed for 1 minute in three

changes of 1X PBS/ 0.1% Tween-20. Five micro liters of 50% glycerol in PBS, 10 mM Tris, pH 8.0, 1 mM EDTA were spotted in each reaction well, and slides were mounted with cover slips. Each reaction well was subsequently analyzed by fluorescence microscopy at 200X power using a B-2A filter (EX 450-490 nm). Positive reactions were scored against 5 an auto fluorescent background obtained with unstained cells or cells stained with secondary reagent alone.

RSV positive reactions were characterized by bright fluorescence punctuated with small inclusions in the cytoplasm of infected cells.

10 Microneutralization Assay:

The procedure used here is described in Johnson et al., 1999, J. Infectious Diseases 180:35-40, the disclosure of which is hereby incorporated by reference in its entirety. Briefly, antibody dilutions were made in triplicate using a 96-well plate. Ten TCID<sub>50</sub> of RSV A MARMS were incubated with serial dilutions of the antibody to be tested for 2 15 hours at 37°C in the wells of a 96-well plate. The antibodies used in the assay comprised the heavy chain of SYNAGIS® or the heavy chain of A4B4, and the light chain of SYNAGIS®, the light chain of A4B4, the light chain of A4B4 with a point mutation, the light chain of L1FR or the light chain of L1FR with point mutations. Mab 13/19 was used as a positive control in the assays. RSV susceptible HEp-2 cells (2.5 x 10<sup>4</sup>) were then added 20 to each well and cultured for 5 days at 37°C in 5% CO<sub>2</sub>. After 5 days, the medium was aspirated and cells were washed and fixed to the plates with 80% methanol and 20% PBS. RSV replication was then determined by F protein expression. Fixed cells were incubated with a biotin-conjugated anti-F protein monoclonal antibody (pan F protein, C-site-specific MAb 133-1H) washed and horseradish peroxidase conjugated avidin was added to the 25 wells. The wells were washed again and turnover of substrate TMB (thionitrobenzoic acid) was measured at 450 nm. The results from the assay for the monoclonal antibodies are shown in Table 25 *infra*.

Results and Discussion:

30 The binding activity of A4B4 was tested by IFA against a MARM obtained by three rounds of selection on HEp-2 cells in the presence of A4B4. A pool of monoclonal antibodies against the fusion, glycoprotein, and nuclear proteins of RSV (Control Pan RSV MAb Pool) was used as a positive control for detection of RSV. Subtyping of RSV MARMs was performed with two monoclonal antibodies that distinguish type A and type B 35 glycoproteins. As summarized in Table 23, lack of binding activity by A4B4 and

SYNAGIS® was demonstrated in both MARMs. Contrasting with lack of binding by A4B4 and SYNAGIS®, binding of the Control Pan RSV MAb Pool was demonstrated for all MARMs tested. Both MARMs were classified as RSV type A. Wild type RSV A/ Long infected HEp-2 cells bound to A4B4 and SYNAGIS®, Pan RSV MAb Pool, and RSV Type 5 A MAb, but failed to react with RSV Type B MAb, as expected.

DNA sequencing analysis of an approximately 800 nucleotide region of the RSV F protein cDNA encompassing the proposed A4B4 epitope revealed mutation at the amino-acid level at position 272 and 262. Table 24 shows the amino acid change in isolates sequenced to date. Although the entire nucleotide sequence of RSV MARMs F protein has 10 not been determined, these results suggest that amino acid 272 and 262 is a critical residue in modulating the binding of A4B4 to its epitope.

The ability of various monoclonal antibodies to neutralize the replication of RSV A MARMs was determined. As shown in Table 25, the ability of the monoclonal antibodies to neutralize the replication of RSV MARMs varied depending upon the amino acid 15 sequence of the heavy chain (HC) and light chain (LC) of the antibody.

Table 23. Characterization of anti-RSV Binding Activity by A4B4, SYNAGIS®, Control Pan RSV MAb Pool (anti-F, G, N proteins), anti-RSV Type A MAb, and anti-RSV Type B MAb by Immunofluorescence Assay (IFA) on RSV A/ Long MARMs.

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| RSV MARM sample | Reactivity w/<br>Synagis® | Reactivity w/<br>Anti-RSV MAb Pool | Reactivity w/<br>Anti-RSV type A MAb | Reactivity w/<br>Anti-RSV type B MAb | Reactivity<br>A4B4 |
|-----------------|---------------------------|------------------------------------|--------------------------------------|--------------------------------------|--------------------|
| MARM #13        | -                         | +                                  | +                                    | -                                    | -                  |
| B9              | -                         | +                                  | +                                    | -                                    | +                  |
| Wt              | +                         | +                                  | +                                    | -                                    | -                  |

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Table 24. Amino acid sequence of a region of the wild type RSV A/ Long and MARMs F Protein.

| Isolate                 | Amino Acid Sequence (Position number) |     |     |     |     |     |     |     |     |     |     |     |
|-------------------------|---------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Wild type RSV<br>Long A | 262                                   | 266 | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 |
|                         | N                                     | I   | T   | N   | D   | Q   | K   | K   | L   | M   | S   | N   |
| MARM #13                | 262                                   | 266 | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 |
|                         | K                                     | I   | T   | N   | D   | Q   | K   | Q   | L   | M   | S   | N   |

Table 25. MARM analysis by Microneutralization Assay

| RSV Microneutralization Assay On RSV A MARMs to A4B4 with RSV Monoclonal Antibody. |                         |
|--|-------------------------|
| Antibody   | K272Q,N262K             |
| HC/LC  | MARM to SYNAGIS® & A4B4 |
| SYNAGIS®/SYNAGIS®  | MARM 13                 |
| A4B4/A4B4  | -                       |
| A4B4/SYNAGIS®  | -                       |
| SYNAGIS®/A4B4  | -                       |
| A4B4/L1FR  | -                       |
| A4B4/L1FR S28R   | -                       |
| A4B4/L1FR S28R, S52F   | -                       |
| A4B4/L1FR-28R, 52F, 93F  | -                       |
| A4B4/A4B428S   | -                       |
| A4B4/A4B452S   | -                       |
| Mab 13/19  | +                       |

+ = neutralization detected; - = no neutralization detected

### 15. EXAMPLE: CLINICAL TRIALS

Antibodies of the invention or fragments thereof tested in *in vitro* assays and animal models may be further evaluated for safety, tolerance and pharmacokinetics in groups of normal healthy adult volunteers. The volunteers are administered intramuscularly, 5 intravenously or by a pulmonary delivery system a single dose of 0.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg or 15 mg/kg of an antibody or fragment thereof which immunospecifically binds to a RSV antigen. Each volunteer is monitored at least 24 hours prior to receiving the single dose of the antibody or fragment thereof and each volunteer will be monitored for at least 48 hours after receiving the dose at a clinical site. Then volunteers are monitored as 10 outpatients on days 3, 7, 14, 21, 28, 35, 42, 49, and 56 postdose.

Blood samples are collected via an indwelling catheter or direct venipuncture using 10 ml red-top Vacutainer tubes at the following intervals: (1) prior to administering the dose of the antibody or antibody fragment; (2) during the administration of the dose of the antibody or antibody fragment; (3) 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 15 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, and 48 hours after administering the dose of the antibody or antibody fragment; and (4) 3 days, 7 days 14 days, 21 days, 28 days, 35 days, 42 days, 49 days, and 56 days after administering the dose of the antibody or antibody fragment. Samples are allowed to clot at room temperature and serum will be collected after centrifugation.

20 The antibody or antibody fragment is partially purified from the serum samples and the amount of antibody or antibody fragment in the samples will be quantitated by ELISA. Briefly, the ELISA consists of coating microtiter plates overnight at 4°C with an antibody that recognizes the antibody or antibody fragment administered to the volunteer. The plates are then blocked for approximately 30 minutes at room temperature with PBS-Tween-0.5% 25 BSA. Standard curves are constructed using purified antibody or antibody fragment, not administered to a volunteer. Samples are diluted in PBS-Tween-BSA. The samples and standards are incubated for approximately 1 hour at room temperature. Next, the bound antibody is treated with a labeled antibody (e.g., horseradish peroxidase conjugated goat-anti-human IgG) for approximately 1 hour at room temperature. Binding of the labeled 30 antibody is detected, e.g., by a spectrophotometer.

The concentration of antibody or antibody fragment levels in the serum of volunteers are corrected by subtracting the predose serum level (background level) from the serum levels at each collection interval after administration of the dose. For each volunteer the pharmacokinetic parameters are computed according to the model-independent approach

(Gibaldi et al., eds., 1982, *Pharmacokinetics*, 2<sup>nd</sup> edition, Marcel Dekker, New York) from the corrected serum antibody or antibody fragment concentrations.

Equivalents

5 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All publications, patents and patent applications mentioned in this specification are  
10 herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

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What is claimed is:

1. An antibody comprising a variable heavy (VH) domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78, wherein said antibody immunospecifically binds to a respiratory syncytial virus (RSV) antigen and said antibody is not SYNAGIS®.
- 10 2. An antibody comprising a variable light (VL) domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.
- 15 3. The antibody of claim 1 which also comprises a VL domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76.
- 20 25 4. An antibody comprising a VH complementarity determining region (CDR)1 having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.
- 30 5. An antibody comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.

6. An antibody comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.

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7. An antibody comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.

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8. An antibody comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165,

SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.

5 9. An antibody comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61, wherein said antibody immunospecifically binds to a RSV antigen and is not SYNAGIS®.

10 10. The antibody of claim 4 further comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114.

15 11. The antibody of claim 4 further comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97.

12. The antibody of claim 4 further comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, and a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97.

13. The antibody of claim 4 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID

NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID 5 NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207.

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14. The antibody of claim 4 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID 15 NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID 20 NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178.

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15. The antibody of claim 4 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61.

16. The antibody of claim 4 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID 30 NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID 35 NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID

NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61.

17. The antibody of claim 10, 11 or 12 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID

NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID 5 NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207.

18. The antibody of claim 10, 11 or 12 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, 10 SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID 15 NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID 20 NO:174, SEQ ID NO:176, or SEQ ID NO:178.

19. The antibody of claim 10, 11 or 12 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

25 20. The antibody of claim 10 or 11 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID 30 NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID 35 NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID

NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

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21. The antibody of claim 12 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID

NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

22. The antibody of claim 5 further comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97.

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23. The antibody of claim 5 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID

NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207.

5        24.      The antibody of claim 5 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, 10      SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID 15      NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178.

25        25.      The antibody of claim 5 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

20        26.      The antibody of claim 5 or 22 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ 25      ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID 30      NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID 35      NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID

NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15,  
5 SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118,  
10 SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170,  
15 SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

27. The antibody of claim 6 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207.

28. The antibody of claim 6 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178.

15 29. The antibody of claim 6 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

30. The antibody of claim 6 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15,

SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102,  
5 SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160,  
10 SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

31. The antibody of claim 7 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178.

32. The antibody of claim 7 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

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33. The antibody of claim 8 further comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID

NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID 5 NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID 10 NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207.

15 34. The antibody of claim 8 further comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

35. The antibody of claim 7 further comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID 20 NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID 25 NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID 30 NO:176, or SEQ ID NO:178, and a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

36. A Fab fragment comprising a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID 35 NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51,

SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78 and a VL domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76, wherein the Fab fragment immunospecifically binds to a RSV antigen and is not a Fab fragment of SYNAGIS®.

37. A fusion protein comprising the antibody of any one of claims 1-9 covalently linked to a heterologous polypeptide.

38. A composition comprising one or more species of antibodies, each species of antibody comprising a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

39. A composition comprising one or more species of antibodies, each species of antibody comprising a VL domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

40. A composition comprising two or more species of antibodies, each species of antibody comprising a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78, wherein each species of antibody immunospecifically binds to a RSV antigen.

41. A composition comprising two or more species of antibodies, each species of antibody comprising a VL domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, 5 SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76, wherein each species of antibody immunospecifically binds to a RSV antigen.

42. The composition of claim 39 or 41, wherein each species of antibody further 10 comprises a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78.

15 43. A composition comprising one or more species of antibodies, each species of antibody comprising a VH CDR1 having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

20 44. A composition comprising two or more species of antibodies, each species of antibody comprising a VH CDR1 having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18, wherein each species of antibody immunospecifically binds to a RSV antigen.

25 45. A composition comprising one or more species of antibodies, each species of antibody comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, wherein each species 30 of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

46. A composition comprising two or more species of antibodies, each species of antibody comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, 35

SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, wherein each species of antibody immunospecifically binds to a RSV antigen.

5 47. A composition comprising one or more species of antibodies, each species of antibody comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

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48. A composition comprising two or more species of antibodies, each species of antibody comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97, wherein each species of antibody immunospecifically binds to a RSV 15 antigen.

49. A composition comprising one or more species of antibodies, each species of antibody comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, wherein each species of antibody

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immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

50. A composition comprising two or more species of antibodies, each species of  
5 antibody comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID  
NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID  
NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95,  
SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110,  
SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120,  
10 SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130,  
SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140,  
SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150,  
SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159,  
SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169,  
15 SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179,  
SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184,  
SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189,  
SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194,  
SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199,  
20 SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204,  
SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, wherein each species of antibody  
immunospecifically binds to a RSV antigen.

51. A composition comprising one or more species of antibodies, each species of  
25 antibody comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID  
NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43,  
SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID  
NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81,  
SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID  
30 NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID  
NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID  
NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID  
NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID  
NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID  
35 NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID

NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

5        52. A composition comprising two or more species of antibodies, each species of antibody comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, 10 SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID 15 NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, wherein each species of antibody immunospecifically binds to a RSV antigen.

20        53. A composition comprising one or more species of antibodies, each species of antibody comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61, wherein each species of antibody immunospecifically binds to a RSV antigen and none of the species of antibodies is SYNAGIS®.

25        54. A composition comprising two or more species of antibodies, each species of antibody comprising a VL CDR3 having an amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61, wherein each species of antibody immunospecifically binds to a RSV antigen.

30        55. A composition comprising one or more of AFFF, Pf12, P12f4, P11d4, A1e9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

56. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

57. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VL domain having an amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

58. The isolated nucleic acid molecule of claim 57, wherein the nucleotide sequence encoding the antibody further comprises a VH domain having an amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78.

59. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VH CDR1 having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18, wherein said antibody immunospecifically binds to a RSV antigen.

60. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VH CDR2 having an amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

61. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VH CDR3 having an amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97, wherein said antibody immunospecifically binds to a 5 RSV antigen and said antibody is not SYNAGIS®.

62. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, 10 SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID 15 NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID 20 NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, wherein said antibody 25 immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

63. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VL CDR2 having an amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, 30 SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID 35 NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID

NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID 5 NO:178, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

64. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody comprising a VL CDR3 having an amino acid sequence of SEQ ID 10 NO:6, SEQ ID NO:16, or SEQ ID NO:61, wherein said antibody immunospecifically binds to a RSV antigen and said antibody is not SYNAGIS®.

65. A vector comprising the nucleic acid molecule as in any one of claims 56-64.  
15 66. The vector of claim 65 further comprising a nucleotide sequence which regulates the expression of the antibody encoded by the nucleic acid molecule.

67. A host cell genetically engineered to express the nucleic acid molecule as in any of claims 56-64.

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68. A host cell comprising the vector of claim 65.

69. A mammalian host cell comprising the nucleic acid molecule as in any of claims 56-64.

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70. A mammalian host cell comprising the vector of claim 65.

71. A method for producing an antibody comprising culturing the host cell of claim 67 under conditions in which the nucleic acid molecule is expressed.

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72. A method for producing an antibody comprising culturing the host cell of claim 68 under conditions in which the nucleic acid molecule is expressed.

73. A pharmaceutical composition comprising at least one antibody as in any of 35 claims 1-9 and a carrier or excipient.

74. The pharmaceutical composition of claim 73 formulated for pulmonary administration.

75. The pharmaceutical composition of claim 73, which is a sustained release 5 formulation.

76. A method of preventing, treating or ameliorating a RSV infection, comprising administering to a mammal in need thereof the pharmaceutical composition of claim 73 in an amount effective to treat, prevent or ameliorate the RSV infection.

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77. A method of preventing, treating or ameliorating a RSV infection, comprising administering to a mammal in need thereof the pharmaceutical composition of claim 75 in an amount effective to treat, prevent or ameliorate the RSV infection.

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78. The method of claim 76, wherein the pharmaceutical composition is administered once a month just prior to or during the RSV season.

79. The method of claim 76, wherein the pharmaceutical composition is administered every two months during the RSV season.

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80. The method of claim 76, wherein the pharmaceutical composition is administered intramuscularly, intravaneously or subcutaneously.

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81. The method of claim 76, wherein the pharmaceutical composition is administered by pulmonary administration.

82. The method of claim 76, wherein the mammal is a human.

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83. The method of claim 76, wherein the mammal is a human infant.

84. The method of claim 76, wherein the mammal is a human infant born prematurely or a human infant at risk of hospitalization for a RSV infection.

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85. The method of claim 82, wherein the human has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency, or acquired immunodeficiency, has had a bone marrow transplant, or is elderly.

5 86. A method for detecting a RSV infection, comprising:

- (a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VH domain having the amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78 and none of the species of antibodies is SYNAGIS®; and
- 10 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

15 87. A method for detecting a RSV infection, comprising:

- (a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VL domain having the amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76 and none of the species of antibodies is SYNAGIS®; and
- 20 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

25 30 35 88. A method for detecting a RSV infection, comprising:

5 (a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using two or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VH domain having the amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, or SEQ ID NO:78; and

10 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

15 89. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using two or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VL domain having the amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74 or SEQ ID NO:76; and

20 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

25 90. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18 and none of the species of antibodies is SYNAGIS®; and

(b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

5 91. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114 and none of the species of antibodies is SYNAGIS®; and

10 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

15 92. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97 and none of the species of antibodies is SYNAGIS®; and

20 (b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

25 93. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VL CDR1 having the amino acid sequence of

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SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207 and none of the species of antibodies is SYNAGIS®; and

(b) comparing the assayed level of the RSV antigen with a control level, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection.

94. A method for detecting a RSV infection, comprising:

(a) assaying the level of a RSV antigen in cells or a tissue sample of 30 a subject using one or more species of antibodies that immunospecifically bind to said RSV antigen, wherein each species of antibody comprises a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID

NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID  
NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID  
NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID  
NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ  
5 ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124,  
SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID  
NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ  
ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147,  
SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID  
10 NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ  
ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170,  
SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID  
NO:178 and none of the species of antibodies is SYNAGIS®; and  
(b) comparing the assayed level of the RSV antigen with a control level,  
15 whereby an increase in the assayed level of RSV antigen compared to  
the control level of the RSV antigen is indicative of a RSV infection.

95. A method for detecting a RSV infection, comprising:  
(a) assaying the level of a RSV antigen in cells or a tissue sample of  
20 a subject using one or more species of antibodies that  
immunospecifically bind to said RSV antigen, wherein each species  
of antibody comprises a VL CDR3 having the amino acid sequence of  
SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61 and none of the  
species of antibodies is SYNAGIS®; and  
(b) comparing the assayed level of the RSV antigen with a control level,  
25 whereby an increase in the assayed level of RSV antigen compared to  
the control level of the RSV antigen is indicative of a RSV infection.

96. A method of preventing treating or ameliorating one or more symptoms  
30 associated with a RSV infection in a mammal, said method comprising administering to said  
mammal a dose of an effective amount of one or more antibodies or fragments thereof that  
immunospecifically bind to one or more RSV antigens, wherein said effective amount is less  
than 15 mg/kg of said antibodies or antibody fragments.

97. The method of claim 96, wherein said antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 M^{-1}$  for said one or more RSV antigens.

98. The method of claim 96 or 97, wherein the dose is less than 5 mg/kg or less.

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99. The method of claim 96 or 97, wherein the dose is 3 mg/kg or less, or 1.5 mg/kg or less.

100. The method of claim 96, wherein said antibodies or antibody fragments are 10 administered by a nebulizer or inhaler.

101. The method of claim 96, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

15 102. The method of claim 96, wherein said antibodies or antibody fragments administered 1, 2, 3, 4 or 5 times during the RSV season.

103. The method of claim 96, wherein at least one of the antibodies is a human or 20 humanized monoclonal antibody.

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104. The method of claim 96, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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105. The method of claim 96, wherein the mammal is a human infant.

106. The method of claim 96, wherein the mammal is a human infant born 35 prematurely or is at risk of hospitalization for a RSV infection.

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107. The method of claim 96, wherein at least one of the antibodies is SYNAGIS®, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

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108. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, comprising administering to said mammal a first dose of an effective amount of one or more antibodies that immunospecifically bind to one or more RSV antigens, wherein said effective amount is a dose of less than 15 mg/kg of 5 said antibodies or antibody fragments, wherein said administration results in an effective serum titer of said antibodies or antibody fragments that is less than 30  $\mu$ g/ml at least 20 days after the administration of said first dose and prior to the administration of a subsequent dose.

10 109. The method of claim 108, wherein said antibodies or antibody fragments bind to said one or more RSV antigens with an affinity constant of at least  $2 \times 10^8 M^{-1}$ .

110. The method of claim 108 or 109, wherein the dose is less than 5 mg/kg or less.

15 111. The method of claim 108 or 109, wherein the dose is 3 mg/kg or less, or 1.5 mg/kg or less.

112. The method of claim 108, wherein said effective serum titer is at least 2 20  $\mu$ g/ml.

113. The method of claim 108, wherein said effective serum titer is less than 30  $\mu$ g/ml at least 30 days after the administration of said first dose and prior to the administration of a subsequent dose.

25 114. The method of claim 108, wherein the dose is 1.5 mg/kg or less and said effective serum titer is at least 2  $\mu$ g/ml at least 30 days after the administration of said first dose and prior to the administration of a subsequent dose.

30 115. The method of claim 108, wherein said antibodies or antibody fragments are administered by a nebulizer or inhaler.

116. The method of claim 108, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

117. The method of claim 108, wherein said antibodies or antibody fragments have half-lives in said human subject of greater than 25 days.

118. The method of claim 108, wherein at least one of the antibodies is a human  
5 or humanized monoclonal antibody.

119. The method of claim 108, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease,  
10 congenital immunodeficiency or acquired immunodeficiency.

120. The method of claim 108, wherein the mammal is a human infant.

121. The method of claim 108, wherein the mammal is a human infant born  
15 prematurely or is at risk of hospitalization for a RSV infection.

122. The method of claim 108, wherein at least one of the antibodies is  
SYNAGIS®, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-  
493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5,  
20 A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

123. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal a first dose of an effective amount of one or more antibodies or fragments thereof  
25 that immunospecifically bind to one or more RSV antigens, wherein said effective amount is approximately 15 mg/kg or less of said antibodies or antibody fragments and an effective serum titer is maintained for at least 20 days after the administration said first dose and prior to the administration of a subsequent dose.

30 124. The method of claim 123, wherein the antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$  for said one or more RSV antigens.

125. The method of claim 123, wherein said effective serum titer is at least 30  
35  $\mu\text{g/ml}$  of said antibodies or antibody fragments.

126. The method of claim 123, wherein said effective serum titer is at least 2 µg/ml of said antibodies or antibody fragments.

127. The method of claim 123, wherein the effective serum titer is maintained for 5 at least 25 days or at least 30 days.

128. The method of claim 123, wherein said antibodies or antibody fragments are administered by a nebulizer or inhaler.

10 129. The method of claim 123, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

130. The method of claim 123, wherein said antibodies or antibody fragments have half-lives in said human subject of greater than 25 days.

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131. The method of claim 123, wherein at least one of the antibodies is a human or humanized monoclonal antibody.

132. The method of claim 123, wherein the mammal is a human subject, a human 20 subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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133. The method of claim 123, wherein the mammal is a human infant.

134. The method of claim 123, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

135. The method of claim 123, wherein at least one of the antibodies is 30 SYNAGIS®, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

136. A sustained release formulation comprising one or more antibodies or 35 fragments thereof that immunospecifically bind to one or more RSV antigens.

137. A pharmaceutical composition comprising one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens formulated for pulmonary delivery.

5 138. The sustained release formulation of claim 136, wherein the antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$  for said one or more RSV antigens.

10 139. The pharmaceutical composition of claim 137, wherein the antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$  for said one or more RSV antigens.

140. The sustained release formulation of claim 136, wherein at least one of the antibodies or antibody fragments is SYNAGIS® or an antigen-binding fragment thereof.

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141. The pharmaceutical composition of claim 137, wherein at least one of the antibodies or antibody fragments is SYNAGIS® or an antigen-binding fragment thereof.

142. The sustained release formulation of claim 136, wherein at least one of said antibodies or antibody fragments is a human or humanized antibody or antibody fragment.

143. The pharmaceutical composition of claim 137, wherein at least one of said antibodies or antibody fragments is a human or humanized antibody or antibody fragment.

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144. The sustained release formulation of claim 136, wherein at least one of said antibodies is SYNAGIS®, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

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145. The pharmaceutical composition of claim 137, wherein at least one of said antibodies at least one of the antibodies is SYNAGIS®, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

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146. The sustained release formulation of claim 136, wherein at least one of said antibodies or antibody fragments has an increased *in vivo* half-life.

147. The pharmaceutical composition of claim 137, wherein at least one of said 5 antibodies or antibody fragments has an increased *in vivo* half-life.

148. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal an effective amount of the sustained release formulation of claim 136.

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149. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to the lungs of said mammal an effective amount of the pharmaceutical composition of claim 137.

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150. The method of claim 148, wherein the sustained release formulation is administered intramuscularly, intravaneously or subcutaneously.

151. The method of claim 148, wherein the sustained release formulation is administered by a nebulizer or inhaler.

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152. The method of claim 149, wherein the pharmaceutical composition is administered intramuscularly, intravaneously or subcutaneously.

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153. The method of claim 149, wherein the pharmaceutical composition is administered by a nebulizer or inhaler.

154. The method of claim 148, wherein the mammal is a human subject.

155. The method of claim 149, wherein the mammal is a human subject.

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156. The method of claim 154, wherein the human subject has had a bone marrow transplant, is elderly, or has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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157. The method of claim 155, wherein the human subject has had a bone marrow transplant, is elderly, or has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

5 158. The method of claim 154, wherein the human subject is an infant.

159. The method of claim 154, wherein the human subject is an infant born prematurely or is at risk of hospitalization for a RSV infection.

10 160. The method of claim 155, wherein the human subject is an infant.

161. The method of claim 155, wherein the human subject is an infant born prematurely or is at risk of hospitalization for a RSV infection.

15 162. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal a first dose of an effective dose of SYNAGIS® or an antigen-binding fragment thereof in a sustained release formulation, wherein said effective dose is approximately 15 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof and an effective serum 20 titer of at least 30 µg/ml is maintained for at least 20 days after the administration said first dose and prior to the administration of a subsequent dose.

163. The method of claim 162, wherein said effective serum titer is maintained for at least 25 days or at least 30 days after the administration of the first dose and prior to the 25 administration of a subsequent dose.

164. The method of claim 162, wherein SYNAGIS® or an antigen-binding fragment thereof is administered by a nebulizer or inhaler.

30 165. The method of claim 162, wherein SYNAGIS® or an antigen-binding fragment thereof is administered intramuscularly, intravaneously or subcutaneously.

166. The method of claim 162, wherein SYNAGIS® or an antigen-binding fragment thereof is administered 1, 2, 3, 4, or 5 times during the RSV season.

167. The method of claim 162, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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168. The method of claim 162, wherein the mammal is a human infant.

169. The method of claim 162, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

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170. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal a first dose of an effective dose of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens with an affinity of at least  $2 \times 10^8$

15 M<sup>1</sup> in a sustained release formulation, wherein said effective dose is approximately 15 mg/kg or less of said antibodies or antibody fragments and an effective serum titer of less than 30 µg/ml is maintained for at least 20 days after the administration said first dose and prior to the administration of a subsequent dose.

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171. The method of claim 170, wherein said effective serum titer is at least 2 µg/ml.

172. The method of claim 170, wherein said effective serum titer is maintained for at least 25 days or at least 30 days after the administration of the first dose and prior to the 25 administration of a subsequent dose.

173. The method of claim 170, wherein said antibodies or antibody fragments are administered by a nebulizer or inhaler.

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174. The method of claim 170, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

175. The method of claim 170, wherein said antibodies or antibody fragments are administered 1, 2, 3, 4, or 5 times during the RSV season.

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176. The method of claim 170, wherein said antibodies or antibody fragments have half-lives in said human subject of greater than 25 days.

177. The method of claim 170, wherein at least one of the antibodies is a human 5 or humanized monoclonal antibody.

178. The method of claim 170, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, 10 congenital immunodeficiency or acquired immunodeficiency.

179. The method of claim 170, wherein the mammal is a human infant.

180. The method of claim 170, wherein the mammal is a human infant born 15 prematurely or is at risk of hospitalization for a RSV infection. .

181. The method of claim 170, wherein at least one of the antibodies is AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4- 20 L1FR-S28R, or A4B4-F52S.

182. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal a dose of an effective amount of one or more antibodies or fragments thereof that 25 immunospecifically bind to one or more RSV antigens and have increased *in vivo* half-lives, wherein said effective amount is a dose approximately 15 mg/kg or less of said antibodies or antibody fragments.

183. The method of claim 182, wherein said antibodies or antibody fragments 30 have an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$  for said one or more RSV antigens.

184. The method of claim 182, wherein the dose is less than 5 mg/kg or less, 3 mg/kg or less, or 1.5 mg/kg or less.

185. The method of claim 182, wherein the increase in *in vivo* half-life is from 21 days to at least 25 days or from 21 days to at least 30 days.

186. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said mammal a dose of an effective amount of HL-SYNAGIS or an antigen-binding fragment thereof, wherein said effective amount is a dose of approximately 15 mg/kg or less of HL-SYNAGIS® or an antigen-binding fragment thereof which results in an effective serum titer that is at least 30 µg/ml at least 30 days after the administration of said first dose and prior 10 to the administration of a subsequent dose.

187. The method of claim 186, wherein said antibodies or antibody fragments are administered by a nebulizer or inhaler.

15 188. The method of claim 186, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

189. The method of claim 186, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human 20 subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

190. The method of claim 186, wherein the mammal is a human infant.

25 191. The method of claim 186, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

192. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to said 30 mammal a dose of an effective amount of one or more antibodies or fragments thereof, wherein said antibodies or fragments thereof immunospecifically bind to one or more RSV antigens and have increased *in vivo* half-lives, and wherein said effective amount is a dose of approximately 15 mg/kg or less of said antibodies or antibody fragments which results in an effective serum titer of less than 30 µg/ml at least 30 days after the administration of said 35 first dose and prior to the administration of a subsequent dose.

193. The method of claim 192, wherein said antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 M^{-1}$  for said one or more RSV antigens.

5 194. The method of claim 192, wherein the effective serum titer is at least 2  $\mu\text{g}/\text{ml}$ , at least 40  $\mu\text{g}/\text{ml}$ , or at least 50  $\mu\text{g}/\text{ml}$ .

195. The method of claim 192, wherein the effective serum titer is at least 30  $\mu\text{g}/\text{ml}$  at least 35 days after the administration of said first dose and prior to the 10 administration of a subsequent dose.

196. The method of claim 192, wherein the effective serum titer is at least 2  $\mu\text{g}/\text{ml}$  at least 35 days after the administration of said first dose and prior to the administration of a subsequent dose.

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197. The method of claim 186, wherein HL-SYNAGIS or an antigen-binding fragment thereof is formulated in a sustained release formulation.

198. The method of claim 192, wherein said antibodies or fragments thereof are 20 formulated in a sustained release formulation.

199. The method of claim 192, wherein said antibodies or fragments thereof are administered by a nebulizer or inhaler.

25 200. The method of claim 192, wherein said antibodies or fragments thereof are administered intramuscularly, intravaneously or subcutaneously.

201. The method of claim 186, wherein HL-SYNAGIS or an antigen-binding fragment thereof has a half-life in said mammalian subject of greater than 25 days.

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202. The method of claim 192, wherein said antibodies or fragments thereof have half-lives in said mammalian subject of greater than 25 days.

203. The method of claim 192, wherein at least one of the antibodies is a human 35 or humanized monoclonal antibody.

204. The method of claim 192, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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205. The method of claim 192, wherein the mammal is a human infant.

206. The method of claim 192, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

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207. The method of claim 192, wherein at least one of said antibodies comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10, SEQ ID NO:18, a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:109, SEQ ID NO:111, or SEQ ID NO:114, a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, SEQ ID NO:83, SEQ ID NO:94 or SEQ ID NO:97, a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39 or SEQ ID NO:47, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:92, SEQ ID NO:95, SEQ ID NO:98, SEQ ID NO:101, SEQ ID NO:104, SEQ ID NO:107, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, or SEQ ID NO:207, a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15,

SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:81, SEQ ID NO:85, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102,  
5 SEQ ID NO:105, SEQ ID NO:108, SEQ ID NO:113, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160,  
10 SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, or SEQ ID NO:178, or a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61.

208. A method of preventing, treating or ameliorating one or more symptoms  
15 associated with a RSV infection in a mammal, said method comprising administering to the lungs of said mammal a first dose of an effective amount of a composition comprising one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein said effective amount results in an effective concentration of at least 20 ng per mg of lung protein at least 20 days after the administration said first dose and prior to  
20 the administration of a subsequent dose.

209. The method of claim 208, wherein said antibodies or antibody fragments have an affinity of at least  $2 \times 10^8 \text{ M}^{-1}$  for said one or more RSV antigens.

25 210. The method of claim 208, wherein said antibodies or antibody fragments have *in vivo* half-lives of greater than 30 days.

211. The method of claim 208, wherein said antibodies or antibody fragments are administered by a nebulizer or inhaler.

30 212. The method of claim 208, wherein said antibodies or antibody fragments are administered intramuscularly, intravaneously or subcutaneously.

213. The method of claim 208, wherein at least one of said antibodies is a human  
35 or humanized monoclonal antibody.

214. The method of claim 208, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

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215. The method of claim 208, wherein the mammal is a human infant.

216. The method of claim 208, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

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217. The method of claim 208, wherein at least one of the antibodies is AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4-L1FR-S28R, or A4B4-F52S.

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218. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a mammal, said method comprising administering to the lungs of said mammal a first dose of an effective amount of a composition comprising SYNAGIS® or a fragment thereof, wherein said effective amount results in an effective concentration of at least 20 ng per mg of lung protein at least 20 days after the administration said first dose and prior to the administration of a subsequent dose.

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219. The method of claim 218, wherein SYNAGIS® or an antigen-binding fragment thereof is administered by a nebulizer or inhaler.

25

220. The method of claim 218, wherein SYNAGIS® or an antigen-binding fragment thereof is administered intramuscularly, intravaneously or subcutaneously.

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221. The method of claim 218, wherein the mammal is a human subject, a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

222. The method of claim 218, wherein the mammal is a human infant..

35

223. The method of claim 218, wherein the mammal is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

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A

DIQMTQSPST LSASVGDRVT ITCKCQLSVGYMH WYQQKPG 40  
CDR L1

KAPKLLIY DTSKLAS GVPSR FSGSGSGTEF TLTSSLQPD 80  
CDR L2

DFATYYC FQGSGYPFT FGGGTKLEIK 106  
CDR L3

B

QVTLRESPA LVKPTQTLTL TCTFSGFSLS TSGMSVG WIR 40  
CDR H1

QPPGKALEWL A DIWWDDKKDYNPSLKS RLT ISKDTSKNQV 80  
CDR H2

VLKVTNMDPA DTATYYCAR SMITNWYFDV W GAGTTVTVSS 120  
CDR H3

FIG. 1

A

DIQMTQSPST LSASVGDRV T TCSASSVGYMH WYQQKPG 40  
CDR L1

KAPKLLIY DTSKLAS GVPSR FSGSGSGTEF TLTSSLQPD 80  
CDR L2

DFATYYC FQGSGPF FGGG TKVEIK 106  
CDR L3

B

QVTLRESGPA LVKPTQTLTL TCTFSGFSLS TSGMSVG WIR 40  
CDR H1

OPPGKALEWL A DIWWDDKDYNPLK RLT ISKDTSKNQV 80  
CDR H2

VLKVTNMDPA DTATYYCAR SMITNWYFDV WGQGTTVTVSS 120  
CDR H3

FIG. 2

## SEQUENCE LISTING

<110> MEDIMMUNE, INC.

<120> Methods of Administering/Dosing Anti-RSV Antibodies for Prophylaxis and Treatment

<130> 10271-049-228

<160> 259

<170> PatentIn version 3.1

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<213> Homo sapiens

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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Ala  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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Ser Met Ile Thr Asn Phe Tyr Phe Asp Val  
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<210> 13

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<213> Homo sapiens

<400> 13

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Ala  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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<400> 18  
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1 5

<210> 19  
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<400> 19  
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<210> 20

<211> 10  
<212> PRT  
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<400> 20  
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1 5 10

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20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys  
100 105

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<210> 23  
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<400> 23  
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1 5

<210> 24  
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<220>  
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1 5 10 15  
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20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser  
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Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Arg Gly Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

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85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

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<210> 28  
 <211> 120  
 <212> PRT  
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 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
 115 120

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 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Met Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys  
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Ser Pro Ser Ser Arg Val Gly Tyr Met His  
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Asp Thr Met Arg Leu Ala Ser  
1 5

<210> 33

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Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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35 40 45  
Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60  
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80  
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95  
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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1 5 10 15

<210> 38  
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys  
100 105

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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

<210> 43

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Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

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<211> 106  
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Asp Arg Val Thr Ile Thr Cys Leu Pro Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Met Tyr Gln Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
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20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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1 5

<210> 51  
<211> 120  
<212> PRT  
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<400> 51  
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1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 52  
<211> 106  
<212> PRT  
<213> Homo sapiens

<400> 52  
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Arg Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 53

<211> 7

<212> PRT

<213> Homo sapiens

<400> 53

Asp Thr Arg Tyr Gln Ser Ser  
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<210> 54

<211> 106

<212> PRT

<213> Homo sapiens

<220>

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<223> VL Domain

<400> 54

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
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Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 55

<211> 120

<212> PRT

<213> Homo sapiens

<400> 55

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Ala  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 56

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> VL Domain

<400> 56

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
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Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
 100 105

<210> 57

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> VL Domain

<400> 57

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Tyr Lys Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 58

<211> 7

<212> PRT

<213> Homo sapiens

<400> 58

Asp Thr Tyr Lys Gln Thr Ser  
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<210> 59

<211> 106

<212> PRT

<213> Homo sapiens

<220>

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<223> VL Domain

<400> 59

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Arg Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 60

<211> 106

<212> PRT

<213> Homo sapiens

<400> 60  
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Phe Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 61

<211> 9

<212> PRT

<213> Homo sapiens

<400> 61

Phe Gln Gly Ser Phe Tyr Pro Phe Thr  
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<210> 62

<211> 106

<212> PRT

<213> Homo sapiens

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<223> VL Domain

<400> 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
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Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Lys Leu Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 63  
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<212> PRT  
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<400> 63  
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<210> 64  
<211> 106  
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<400> 64  
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 65  
<211> 106  
<212> PRT  
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<400> 65  
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
 100 105

<210> 66  
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 <212> PRT  
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<400> 66  
 Asp Thr Phe Arg Leu Ala Ser  
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<210> 67  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 67  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Ala  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 68  
 <211> 106  
 <212> PRT  
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<400> 68  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Tyr Arg His Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 69  
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<212> PRT  
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<400> 69  
Asp Thr Tyr Arg His Ser Ser  
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<210> 70  
<211> 106  
<212> PRT  
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<400> 70  
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Tyr Lys Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 71  
<211> 106  
<212> PRT  
<213> Homo sapiens

<400> 71  
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Ser Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Phe Phe His Arg Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 72

<211> 10

<212> PRT

<213> Homo sapiens

<400> 72

Ser Leu Ser Ser Val Gly Tyr Met His  
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<210> 73

<211> 7

<212> PRT

<213> Homo sapiens

<400> 73

Asp Thr Phe Phe His Arg Ser  
1 5

<210> 74

<211> 106

<212> PRT

<213> Homo sapiens

<400> 74

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Leu Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95

Phe Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 75

<211> 7

<212> PRT

<213> Homo sapiens

<400> 75

Asp Thr Leu Leu Asp Ser  
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<210> 76  
<211> 106  
<212> PRT  
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<400> 76  
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
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Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
20 25 30  
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45  
Asp Thr Ser Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60  
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80  
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95  
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

<210> 77  
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<400> 77  
Asp Thr Ser Phe Leu Asp Ser  
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<210> 78  
<211> 120  
<212> PRT  
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<400> 78  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Ala  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 79  
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<400> 79  
Asp Met Ile Thr Asn Phe Tyr Phe Asp Val  
1 5 10

<210> 80  
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<212> PRT  
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<400> 80  
Lys Cys Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 81  
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<400> 81  
Asp Thr Ser Tyr Leu Ala Ser  
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<210> 82  
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<400> 82  
Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser Leu Lys Ser  
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<210> 83  
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<400> 83  
Asp Met Ile Thr Asn Trp Tyr Phe Asp Val  
1 5 10

<210> 84  
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<212> PRT  
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<400> 84  
Lys Cys Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 85  
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Asp Thr Ser Tyr Leu Ser Ser  
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<210> 86  
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<400> 86  
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<400> 87  
Lys Cys Gln Leu Arg Val Gly Tyr Met His  
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<210> 88  
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<400> 88  
Asp Thr Lys Lys Leu Ser Ser  
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<210> 89  
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<400> 89  
Lys Leu Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 90  
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<400> 90  
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<400> 94  
Ser Met Ile Phe Asn Trp Tyr Phe Asp Val  
1 5 10

<210> 95  
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Lys Leu Gln Ser Arg Val Gly Tyr Met His  
1 5 10

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<400> 96  
Asp Thr Phe Lys Leu Ser Ser  
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<210> 97  
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Ser Met Ile Phe Asn Phe Tyr Phe Asp Val  
1 5 10

<210> 98  
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<400> 98  
Lys Leu Gln Leu Arg Val Gly Tyr Met His  
1 5 10

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Asp Thr Phe Tyr Leu Ala Ser  
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<210> 102  
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<210> 103  
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1 5 10 15

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<400> 104  
Lys Leu Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 105  
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<400> 105  
Asp Thr Ser Gly Leu Ala Ser  
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<210> 106  
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Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser Leu Lys Ser  
1 5 10 15

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Lys Leu Ser Ser Arg Val Gly Tyr Met His  
1 5 10

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1 5 10 15

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<400> 115  
Lys Cys Ser Ser Ser Val Gly Tyr Met His  
1 5 10

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Asp Thr Arg Gly Leu Ala Ser  
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Lys Cys Ser Leu Arg Val Gly Tyr Met His  
1 5 10

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Asp Thr Arg Lys Leu Pro Ser  
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<400> 119  
Lys Cys Ser Leu Arg Val Gly Tyr Met His  
1 5 10

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<400> 120  
Ser Leu Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 121  
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<400> 121  
Asp Thr Met Lys Leu Ala Ser  
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Ser Leu Ser Ser Ser Val Gly Tyr Met His  
1 5 10

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<400> 123  
Asp Thr Ser Arg Leu Ala Ser  
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<210> 124  
<211> 7  
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<400> 124  
Asp Thr Ser Leu Leu Ala Ser  
1 5

<210> 125  
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<400> 125  
Ser Leu Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 126  
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<400> 126  
Asp Thr Ser Leu Leu Asp Ser  
1 5

<210> 127  
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<400> 127  
Ser Cys Gln Leu Ser Val Gly Tyr Met His  
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<400> 128  
Asp Thr Ser Lys Leu Asp Ser  
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<400> 129  
Ser Cys Gln Ser Ser Val Gly Tyr Met His  
1 5 10

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Ser Cys Gln Ser Arg Val Gly Tyr Met His  
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<400> 131  
Asp Thr Leu Lys Leu Asp Ser  
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<210> 132  
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Ser Cys Gln Leu Arg Val Gly Tyr Met His  
1 5 10

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<400> 133  
Asp Thr Leu Leu Leu Ala Ser  
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<400> 134  
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Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
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 Gly Lys  
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 35 40 45  
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
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 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
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 Gly Lys  
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 35 40 45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
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 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
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 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
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 Asn Arg Gly Glu Cys  
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 35 40 45  
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 50 55 60  
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 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
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 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
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 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
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 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
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 Gly Lys  
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 35 40 45  
 Asp Thr Phe Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
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 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Ile His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 215  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 215  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Arg Gly Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205

Asn Arg Gly Glu Cys  
 210

<210> 216  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens

<400> 216  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 217  
 <211> 213

<212> PRT  
 <213> Homo sapiens

<400> 217  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Met Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 218  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 218  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 219  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
 <400> 219  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 220  
<211> 450  
<212> PRT  
<213> Homo sapiens

<400> 220  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125  
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140  
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160  
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175  
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190  
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205  
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220  
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
225 230 235 240  
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
245 250 255  
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
260 265 270  
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
275 280 285  
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 221  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 221  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 222  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 222  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 223  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 223  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30 35

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205

Asn Arg Gly Glu Cys  
 210

<210> 224  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens

<400> 224  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser  
 50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 225  
 <211> 213

<212> PRT  
 <213> Homo sapiens

<400> 225  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Leu Pro Ser Ser Arg Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205

Asn Arg Gly Glu Cys  
 210

<210> 226

<211> 450

<212> PRT

<213> Homo sapiens

<400> 226  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 227  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
 <400> 227  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 228  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens

<400> 228  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 229  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 229  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Arg Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 230  
 <211> 451  
 <212> PRT  
 <213> Homo sapiens  
 <400> 230  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser  
 20 25 30  
 Gly Met Ser Val Gly Tyr Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu  
 35 40 45  
 Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro  
 50 55 60  
 Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln  
 65 70 75 80  
 Val Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr  
 85 90 95  
 Tyr Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly  
 100 105 110  
 Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser  
 115 120 125  
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala  
 130 135 140  
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val  
 145 150 155 160  
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala  
 165 170 175  
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val  
 180 185 190  
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His  
 195 200 205  
 Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys  
 210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly  
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met  
 245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His  
 260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val  
 275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr  
 290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly  
 305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile  
 325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val  
 340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser  
 355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu  
 370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro  
 385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val  
 405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met  
 420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser  
 435 440 445

Pro Gly Lys  
 450

<210> 231  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 231  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 232  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 232  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 233  
 <211> 213

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 233

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
100 105 110Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
115 120 125Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
130 135 140Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
145 150 155 160Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
165 170 175Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
180 185 190Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
195 200 205Asn Arg Gly Glu Cys  
210

&lt;210&gt; 234

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 234

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 235

<211> 213

<212> PRT

<213> Homo sapiens

<400> 235

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Tyr Lys Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205

Asn Arg Gly Glu Cys  
 210

<210> 236  
<211> 450  
<212> PRT  
<213> Homo sapiens

<400> 236  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
  
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
  
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
  
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125  
  
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140  
  
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160  
  
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175  
  
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190  
  
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205  
  
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220  
  
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
225 230 235 240  
  
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
245 250 255  
  
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
260 265 270  
  
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
275 280 285  
  
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 237

<211> 213

<212> PRT

<213> Homo sapiens

<400> 237

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Arg Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95

Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 238  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 238  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 239  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 239  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 240  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 240  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Ser Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 241  
 <211> 213

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 241

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
20 25 30His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Phe Tyr Pro Phe Thr  
85 90 95Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
100 105 110Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
115 120 125Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
130 135 140Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
145 150 155 160Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
165 170 175Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
180 185 190Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
195 200 205Asn Arg Gly Glu Cys  
210

&lt;210&gt; 242

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 242

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95

Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 243  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
 <400> 243  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 244  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens

<400> 244  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Ile Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 245  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
 <400> 245  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 246  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 246  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445

Gly Lys  
 450

<210> 247  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 247  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45

Asp Thr Phe Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210  
 <210> 248  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens  
 <400> 248  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
435 440 445

Gly Lys  
450

<210> 249  
<211> 214

<212> PRT  
<213> Homo sapiens

<400> 249  
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45

Asp Thr Tyr Arg His Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe  
85 90 95

Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala  
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly  
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala  
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln  
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser  
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr  
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser  
195 200 205

Phe Asn Arg Gly Glu Cys  
210

<210> 250

<211> 450

<212> PRT

<213> Homo sapiens

<400> 250  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 251  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
 <400> 251  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Phe His Arg Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 252  
 <211> 450  
 <212> PRT  
 <213> Homo sapiens

<400> 252  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
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<212> DNA

<213> Artificial

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<223> Description of Artificial Sequence: Primer

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26

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(71) Applicant: MEDIUMMUNE, INC [US/US]; 35 West Watkins Mill Road, Gaithersburg, MD 20878 (US).

(72) Inventors: YOUNG, James, F.; 18309 Mockingbird Lane, Darnestown, MD 20874 (US). KOENIG, Scott; 10901 Ralson Road, Rockville, MD 20852 (US). JOHNSON, Leslie, S.; 20147 Laurel Hill Way, Germantown, MD 20874 (US).

(74) Agent: INSOGNA, Anthony, M.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

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Published:

— with international search report

(88) Date of publication of the international search report:  
19 June 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/043660 A3

(54) Title: METHODS OF ADMINISTERING/DOSING ANTI-RSV ANTIBODIES FOR PROPHYLAXIS AND TREATMENT

(57) **Abstract:** The present invention encompasses novel antibodies and fragments thereof which immunospecifically bind to one or more RSV antigens and compositions comprising said antibody fragments. The present invention encompasses methods preventing respiratory syncytial virus (RSV) infection in a human, comprising administering to said human a prophylactically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein a certain serum titer of said antibodies or antibody fragments is achieved in said human subject. The present invention also encompasses methods for treating or ameliorating symptoms associated with a RSV infection in a human, comprising administering to said human a therapeutically effective amount of one or more antibodies or fragments thereof that immunospecifically bind to one or more RSV antigens, wherein a certain serum titer of said antibodies or antibody fragments is achieved in said human subject. The present invention further encompasses compositions comprising antibodies or fragments thereof that immunospecifically bind to a SRV antigen, and methods using said compositions for detection or diagnosis a RSV infection.



**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US01/44807

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Continuation Sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: Please See Continuation Sheet
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  

The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Note that all claims reciting the trademark SYNAGIS and HL-SYNAGIS will be searched only in part regarding the antibodies that are non-SYNAGIS, or excluded from the search (claims 140, 141, 162-169, 186-191, 197, 201 and 218-223). SYNAGIS and HL-SYNAGIS antibodies cannot be searched because they are trademarks, whose exact amino acid sequences are not disclosed in this application and can be changed by the owner. Claims in Group 43 will only be searched in part based on a text name search since amino acid sequences have not been provided.

Group 1, claim(s) 1, 37, 38, 40, 56, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200, 202-206 and 208-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VH domain* selected from the group consisting of 14 sequences. The 14 sequences represent 14 special technical features.

Group 2, claim(s) 2, 37, 39, 41, 57, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200, 202-206 and 208-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VL domain* selected from the group consisting of 23 sequences. The 23 sequences represent 23 special technical features.

Group 3, claim(s) 3, 36, 37, 42, 58, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-206 and 208-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VH and VL domain* selected from the group consisting of 14 and 23 sequences, respectively, for a total of 322 possible combinations. The 322 sequence combinations represent 322 special technical features.

Group 4, claim(s) 4, 37, 43, 44, 59, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VH CDR1 domain* selected from the group consisting of 3 sequences. The 3 sequences represent 3 special technical features.

Group 5, claim(s) 5, 37, 45, 46, 60, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VH CDR2 domain* selected from the group consisting of 16 sequences. The 16 sequences represent 16 special technical features.

Group 6, claim(s) 6, 37, 47, 48, 53, 54, 61, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VH CDR3 domain* selected from the group consisting of 8 sequences. The 8 sequences represent 8 special technical features.

Group 7, claim(s) 7, 37, 49, 50, 62, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VL CDR1 domain* selected from the group consisting of 80 sequences. The 80 sequences represent 80 special technical features.

Group 8, claim(s) 8, 37, 51, 52, 63, 65-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VL CDR2 domain* selected from the group consisting of 58 sequences. The 58 sequences represent 58 special technical features.

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Group 9, claim(s) 9, 37, 53, 54, 64-85, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody, nucleic acid encoding the antibody, vectors, host cells, methods of producing, pharmaceuticals and methods of treating, wherein the antibody has a *VL CDR3* domain selected from the group consisting of 3 sequences. The 3 sequences represent 3 special technical features.

Group 10, claim(s) 10, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VH CDR2*, selected from the groups consisting of 3 and 16 sequences, respectively, for a total of 48 possible sequence combinations. The 48 combinations represent 48 distinct inventions.

Group 11, claim(s) 11, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VH CDR3*, selected from the groups consisting of 3 and 8 sequences, respectively, for a total of 24 possible sequence combinations. The 24 combinations represent 24 special technical features.

Group 12, claim(s) 12, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1*, *VH CDR2* and *VH CDR3*, selected from the groups consisting of 3, 16 and 8 sequences, respectively, for a total of 384 possible sequence combinations. The 384 combinations represent 384 special technical features.

Group 13, claim(s) 13, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VL CDR1*, selected from the groups consisting of 3 and 80 sequences, respectively, for a total of 240 possible sequence combinations. The 240 combinations represent 240 special technical features.

Group 14, claim(s) 14, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VL CDR2*, selected from the groups consisting of 3 and 58 sequences, respectively, for a total of 174 possible sequence combinations. The 174 combinations represent 174 special technical features.

Group 15, claim(s) 15, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VL CDR3*, selected from the groups consisting of 3 and 3 sequences, respectively, for a total of 9 possible sequence combinations. The 9 combinations represent 9 special technical features.

Group 16, claim(s) 16, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody comprises *VH CDR1* and *VL CDR1*, *VL CDR2* and *VL CDR3*, selected from the groups consisting of 3, 80, 58 and 3 sequences, respectively, for a total of 41,760 possible sequence combinations. The 41,760 combinations represent 41,760 special technical features.

Group 17, claim(s) 17, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claims 10, 11 or 12, and further comprises *VL CDR1* selected from the group consisting of 80 sequences. For the antibodies of claims 10, 11 and 12 with the *VL CDR1*, there are 3840, 1920 and 30,720 possible sequence combinations, respectively. The total number of possible sequence combinations is 36,480. The 36,480 combinations represent 36,480 special technical features.

Group 18, claim(s) 18, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claims 10, 11 or 12, and further comprises *VL CDR2* selected from the group consisting of 58 sequences. For the antibodies of claims 10, 11 and 12 with the *VL CDR2*, there are 2784, 1392 and 22,272 possible sequence combinations, respectively. The total number of possible sequence combinations is 26,448. The 26,448 combinations represent 26,448 special technical features.

Group 19, claim(s) 19, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claims 10, 11 or 12, and further comprises *VL CDR3* selected from the group consisting of 3 sequences. For the antibodies of claims 10, 11 and 12 with the *VL CDR3*, there are 144, 72 and 1152 possible sequence combinations, respectively. The total number of possible sequence combinations is 1,368. The 1,368 combinations represent 1,368 special technical features.

Group 20, claim(s) 20, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claims 10 or 11, and further comprises *VL CDR1*, *VL CDR2* and *VL CDR3*, selected from the groups consisting of 80, 58 and 3 sequences, respectively. For the antibodies of claims 10 or 11 with the *VL CDR1*, *VL CDR2* and *VL CDR3*, there are 668,160 and 334,080 possible sequence

## INTERNATIONAL SEARCH REPORT

combinations, respectively. The total number of possible sequence combinations is 1,002,240. The 1,002,240 combinations represent 1,002,240 special technical features.

Group 21, claim(s) 21, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 12, and further comprises *VL CDR1*, *VL CDR2* and *VL CDR3*, selected from the groups consisting of 80, 58 and 3 sequences, respectively. For the antibody of claim 12 with the *VL CDR1*, *VL CDR2* and *VL CDR3*, there are 5,345,280 possible sequence combinations, respectively. The 5,345,280 combinations represent 5,345,280 special technical features.

Group 22, claim(s) 22, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 5, and further comprises *VH CDR3*, selected from the group consisting of 8 sequences. For the antibody of claim 5 with the *VH CDR3*, there are 128 possible sequence combinations. The 128 combinations represent 128 special technical features.

Group 23, claim(s) 23, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 5, and further comprises *VL CDR1*, selected from the group consisting of 80 sequences. For the antibody of claim 5 with the *VL CDR1*, there are 1280 possible sequence combinations. The 1280 combinations represent 1280 special technical features.

Group 24, claim(s) 24, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 5, and further comprises *VL CDR2*, selected from the group consisting of 58 sequences. For the antibody of claim 5 with the *VH CDR2*, there are 928 possible sequence combinations. The 928 combinations represent 928 special technical features.

Group 25, claim(s) 25, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 5, and further comprises *VL CDR3*, selected from the group consisting of 3 sequences. For the antibody of claim 5 with the *VL CDR3*, there are 48 possible sequence combinations. The 48 combinations represent 48 special technical features.

Group 26, claim(s) 26, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claims 5 or 22, and further comprises *VL CDR1*, *VL CDR2* and *VL CDR3*, selected from the groups consisting of 80, 58 and 3 sequences, respectively. For the antibody of claims 5 or 22 with the *VL CDR1*, *VL CDR2* and *VL CDR3*, there are 222,720 and 1,781,760 possible sequence combinations, respectively. The total number of possible sequence combinations is 2,004,480. The 2,004,480 combinations represent 2,004,480 special technical features.

Group 27, claim(s) 27, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 6, and further comprises *VL CDR1*, selected from the group consisting of 80 sequences. For the antibody of claim 6 with the *VL CDR1*, there are 640 possible sequence combinations. The 640 combinations represent 640 special technical features.

Group 28, claim(s) 28, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 6, and further comprises *VL CDR2*, selected from the group consisting of 58 sequences. For the antibody of claim 6 with the *VL CDR2*, there are 464 possible sequence combinations. The 464 combinations represent 464 special technical features.

Group 29, claim(s) 29, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 6, and further comprises *VL CDR3*, selected from the group consisting of 3 sequences. For the antibody of claim 6 with the *VL CDR3*, there are 3 possible sequence combinations. The 24 combinations represent 24 special technical features.

Group 30, claim(s) 30, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 6, and further comprises *VL CDR1*, *VL CDR2* and *VL CDR3*, selected from the groups consisting of 80, 58 and 3 sequences, respectively. For the antibody of claim 6 with the *VL CDR1*, *VL CDR2* and *VL CDR3*, there are 111,360 possible sequence combinations, respectively. The 111,360 combinations represent 111,360 special technical features.

Group 31, claim(s) 31, 33, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 7, and further comprises *VL CDR2*, selected from the group consisting of 58 sequences. For the antibody of claim 7 with the *VL CDR2*, there are 4640 possible sequence combinations. The 4640 combinations represent 4640 special technical features.

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Group 32, claim(s) 32, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 7, and further comprises *VL CDR3*, selected from the group consisting of 3 sequences. For the antibody of claim 7 with the *VL CDR3*, there are 240 possible sequence combinations. The 240 combinations represent 240 special technical features.

Group 33, claim(s) 34, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 8, and further comprises *VL CDR3*, selected from the group consisting of 3 sequences. For the antibody of claim 8 with the *VL CDR3*, there are 84 possible sequence combinations. The 84 combinations represent 84 special technical features.

Group 34, claim(s) 35, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-216, drawn to an antibody and method of treating with the antibody, wherein the antibody is the antibody of claim 7, and further comprises *VL CDR2* and *VL CDR3*, selected from the groups consisting of 58 and 3 sequences, respectively. For the antibody of claim 7 with the *VL CDR2* and *VL CDR3*, there are 13,920 possible sequence combinations. The 13,920 combinations represent 13,920 special technical features.

Group 35, claim(s) 86 and 88, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VH domain* selected from the group consisting of 14 sequences. The 14 sequences represent 14 special technical features.

Group 36, claim(s) 87 and 89, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VL domain* selected from the group consisting of 23 sequences. The 23 sequences represent 23 special technical features.

Group 37, claim(s) 90, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VH CDR1* selected from the group consisting of 3 sequences. The 3 sequences represent 3 special technical features.

Group 38, claim(s) 91, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VH CDR2* selected from the group consisting of 16 sequences. The 16 sequences represent 16 special technical features.

Group 39, claim(s) 92, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VH CDR3* selected from the group consisting of 8 sequences. The 8 sequences represent 8 special technical features.

Group 40, claim(s) 93, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VL CDR1* selected from the group consisting of 80 sequences. The 80 sequences represent 80 special technical features.

Group 41, claim(s) 94, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VL CDR2* selected from the group consisting of 58 sequences. The 58 sequences represent 58 special technical features.

Group 42, claim(s) 95, drawn to a method for detecting a RSV infection using an antibody, wherein the antibody has a *VL CDR3* selected from the group consisting of 3 sequences. The 3 sequences represent 3 special technical features.

Group 43, claim(s) 55, 96-139, 142-161, 170-185, 192-196, 198-200, 202-206 and 208-217, drawn to an antibody and method for treating with the antibody, wherein the antibody is selected from the group consisting of 24 antibody names. Lacking evidence to the contrary, the 24 names have different amino acid sequence and encode 24 different antibodies and therefore represent 24 special technical features.

The inventions listed as Groups 1-43 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups 1-34 and the numerous sequence combinations thereof comprise different amino acid sequences and therefore lack the same special technical feature. The antibodies used in the methods of Groups 35-42 lack the same special technical feature for the same reason.

Groups 1 and 35 are drawn to antibody/method of treating, and method of detecting, respectively. The antibodies used in both methods comprise the same set of sequences. Groups 1 and 35 lack the same special technical feature because PCT Annex B of Administrative Instructions only allows for one method of use to be joined with the main invention. In the same way, Groups 2 and 36, 4 and 37, 5 and 38, 6 and 39, 7 and 40, 8 and 41, and 9 and 42 lack the same special technical feature.

Collectively, groups 3 and 10-34 lack the same special technical feature with groups 35-42. The antibodies used in the methods of treating (groups 3 and 10-34) and detecting (groups 35-42) are not comprised of the same sets of amino acid sequences.

Groups 1-34 and group 43 lack the same special technical feature because it cannot be determined if the antibodies claimed in group 43 are the same as claimed in groups 1-34. For the same reasons, groups 35-42 and group 43 lack the same special technical feature.

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Applicant is invited to clarify the identity of the antibodies. If the antibodies of group 43 are the same as those of groups 1-34, then group 43 will be rejoined appropriately to groups 1-34, but group 43 will not be joined with groups 35-42 because the PCT Annex B of Administrative Instructions only allows for one method of use to be joined with the main invention.

The number of inventions in groups 1-2, 4-9 and 35-43 was calculated by adding the number of different sequences listed in each claim. The number of inventions in groups 3 and 10-34 was calculated by multiplying the number of sequences in one domain by the number in another domain, resulting in the total number of possible combinations between domains. For example, group 3 is drawn to an antibody with a VH domain selected from 14 sequences, and a VL domain selected from 23 sequences. The number of VH sequences was multiplied by the number of VL sequences, resulting in 322 possible combinations of VH and VL domains for group 3. Similar calculations were carried out for groups 10-34. The total number of inventions is the sum of each group's inventions.

If Applicant declines paying additional fees for the search of additional inventions, Group 1 will be searched with respect to the first named sequence, SEQ ID NO: 7. If Applicant pays for additional inventions, groups that have multiple sequences will be searched with respect to the first named sequence, unless otherwise instructed.

**Continuation of Box II Item 3:**

21, 96-106, 108-121, 123-134, 136-139, 142-143, 146-161, 170-180, 182-185, 192-196, 198-200 and 202-106

**Continuation of B. FIELDS SEARCHED Item 3:**

EAST, SPTREMBL\_19, SWISSPROT\_40, PIR-71, A\_GENESEQ\_032802, ISSUED\_PATENTS\_AA  
search terms: young, koenig, johnson, respiratory syncytial virus, rsv, antibodies, method, treatment, prevention, ameliorate, administer, humanized

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